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**FASTTRACK CLINICAL RESEARCH**
*Heart failure and cardiomyopathies*

# NT-proBNP and high intensity care for acute heart failure: the STRONG-HF trial

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**See the editorial comment for this article 'Making STRONGer the transition phase: personalized GDMT through NT-proBNP monitoring', by A. Bayes-Genis and D. Pascual-Figal, https://doi.org/10.1093/eurheartj/ehad356.**

## Abstract

**Aims** STRONG-HF showed that rapid up-titration of guideline-recommended medical therapy (GRMT), in a high intensity care (HIC) strategy, was associated with better outcomes compared with usual care. The aim of this study was to assess the role of *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline and its changes early during up-titration.

**Methods and results** A total of 1077 patients hospitalized for acute heart failure (HF) and with a >10% NT-proBNP decrease from screening (i.e. admission) to randomization (i.e. pre-discharge), were included. Patients in HIC were stratified by further NT-proBNP changes, from randomization to 1 week later, as decreased (≥30%), stable (<30% decrease to ≤10% increase), or increased (>10%). The primary endpoint was 180-day HF readmission or death. The effect of HIC vs. usual care was independent of baseline NT-proBNP. Patients in the HIC group with stable or increased NT-proBNP were older, with more severe acute HF and worse renal and liver function. Per protocol, patients with increased NT-proBNP received more diuretics and were up-titrated more slowly during the first weeks after discharge. However, by 6 months, they reached 70.4% optimal GRMT doses, compared with 80.3% for those with NT-proBNP decrease. As a result, the primary endpoint at 60 and 90 days occurred in 8.3% and 11.1% of patients with increased NT-proBNP vs. 2.2% and 4.0% in those with decreased NT-proBNP ($P = 0.039$ and $P = 0.045$, respectively). However, no difference in outcome was found at 180 days (13.5% vs. 13.2%; $P = 0.93$).

**Conclusion** Among patients with acute HF enrolled in STRONG-HF, HIC reduced 180-day HF readmission or death regardless of baseline NT-proBNP. GRMT up-titration early post-discharge, utilizing increased NT-proBNP as guidance to increase diuretic

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therapy and reduce the GRMT up-titration rate, resulted in the same 180-day outcomes regardless of early post-discharge NT-proBNP change.

## Structured Graphical Abstract

### Key Question

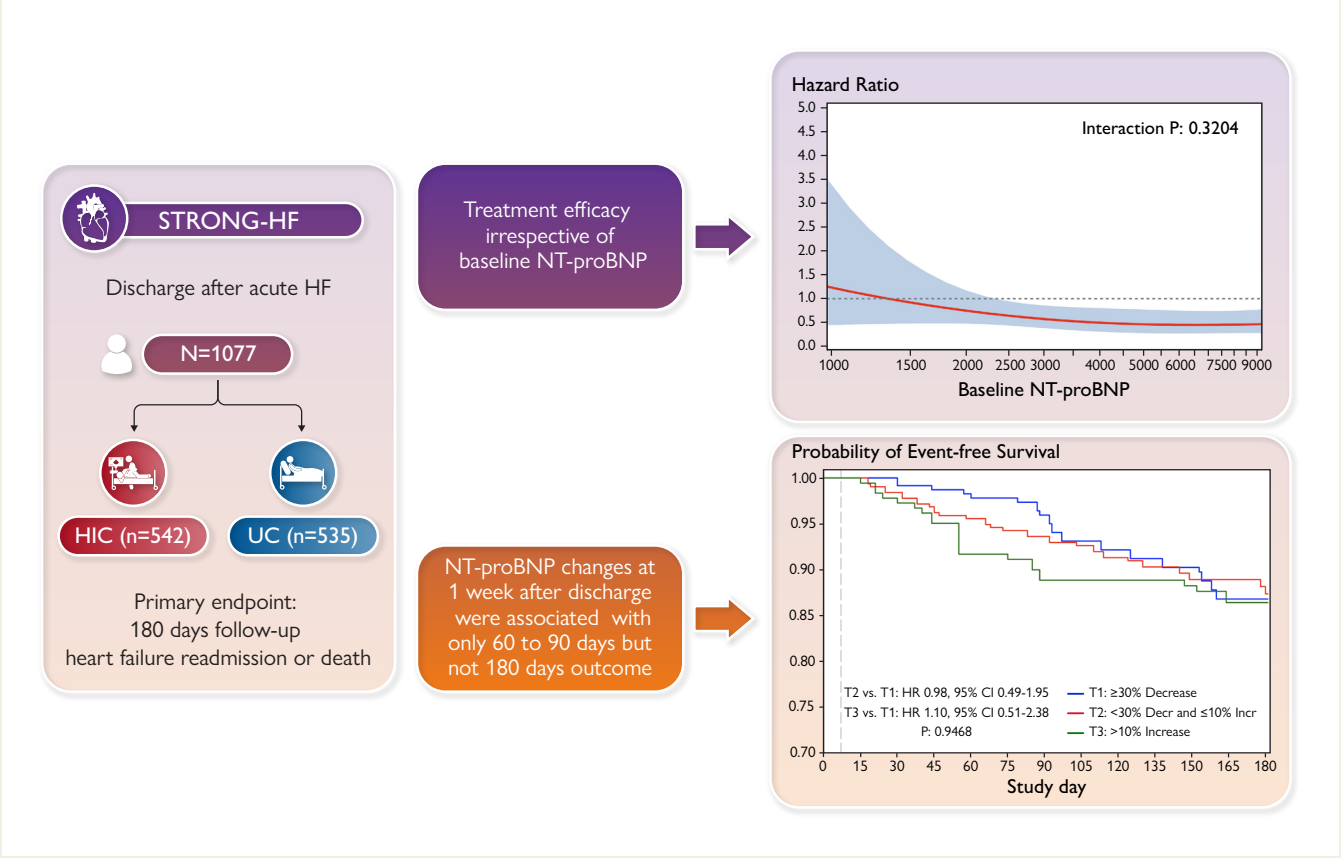
In patients recently hospitalized for acute heart failure, is high intensity care with rapid guideline-recommended medical therapy (GRMT) titration associated with better outcomes compared to usual care irrespective of NT-proBNP concentrations? Are NT-proBNP changes early after discharge related to clinical outcomes?

### Key Finding

In STRONG-HF, a high-intensity care strategy was more efficient than usual care in reducing clinical events regardless of baseline NT-proBNP concentrations. In patients receiving high-intensity care, NT-proBNP increase early after discharge was associated with slower GRMT titration and poorer outcome at 90 days, but not at 180 days.

### Take Home Message

In patients with acute heart failure, rapid up-titration of oral medications and close follow-up early after discharge is beneficial, compared to usual care, regardless of NT-proBNP levels. Post-discharge measurements of NT-proBNP plasma concentrations are useful for medical treatment dose changes, but are not associated with 180 days outcome.




The role of NT-proBNP in patients receiving high intensity care (HIC) after hospital admission for acute heart failure. This analysis from the STRONG-HF trial includes 1077 patients. The treatment effect of a HIC strategy vs. usual care (UC) reduced the primary endpoint regardless of baseline NT-proBNP concentrations. In the 542 patients included in the HIC group, an increase in NT-proBNP levels was associated with a poorer outcome up to 90-day follow-up, but not at 180 days. CI, confidence interval; HF, heart failure; HR, hazard ratio; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide.

**Keywords** Heart failure • Medical therapy • Biomarkers

# Introduction

*N*-terminal pro-B-type natriuretic peptide (NT-proBNP) has a major role in the diagnosis and risk stratification of patients with heart failure (HF).[1–3] However, its role in the titration of guideline-recommended medical therapy (GRMT) remains unsettled. The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) study[4–6] showed the efficacy and safety of a high intensity care (HIC) regimen vs. usual care (UC) in patients recently hospitalized for acute HF. *N*-terminal pro-B-type natriuretic peptide measurements had a major role in this trial. First, they were used as enrolment criteria as patients had to have NT-proBNP concentrations at screening >2500 pg/mL with >10% decrease between screening and randomization with values >1500 pg/mL at randomization. Second, NT-proBNP measurements were repeated at 1-, 2-, 3-, and 6-week follow-up visits in the HIC regimen group and physicians were recommended not to up-titrate beta-blocker and to increase diuretic dose when NT-proBNP concentrations were >10% higher than at pre-discharge. In the pre-specified subgroup analysis of STRONG-HF, there was a trend towards a larger benefit of HIC vs. UC in patients with NT-proBNP levels above median, but without significant interaction.[4]

Our present analysis tested two main hypotheses. First, the safety and efficacy of HIC vs. UC may have been different across patients with different NT-proBNP values at baseline. Second, we hypothesized that a HIC strategy of diuretic dose escalation and slower titration of GRMT in response to NT-proBNP increase might have mitigated, if not neutralized, the prognostic impact of early NT-proBNP changes on long-term outcome. Thus, the aim of this study was to examine the relation between baseline NT-proBNP levels and the efficacy of HIC vs. UC, as well as the prognostic significance of changes in NT-proBNP concentrations during follow-up in the HIC group.

# Methods

## Study design

The design and main results of the STRONG-HF trial have been reported previously.[4,5] Briefly, this multicentre, open-label, randomized trial compared a HIC strategy with early up-titration of renin-angiotensin system (RAS) modulators [angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARB) in patients intolerant to ACEi, or angiotensin receptor-neprilysin inhibitor (ARNI)], beta-blockers, and mineralocorticoid receptor antagonists (MRA), vs. UC, among 1078 patients admitted to hospital for acute HF (within 72 h before screening) and not treated with full doses of medical therapy for HF. Included patients were haemodynamically stable, had any left ventricular ejection fraction (LVEF), and had high NT-proBNP values at screening (>2500 pg/mL) with a >10% decrease in value between screening and randomization (within 2 days before anticipated discharge) that remained >1500 pg/mL. Patients in the HIC group had follow-up visits at 1, 2, 3, and 6 weeks after randomization, including physical examination to assess congestion and laboratory assessments, including NT-proBNP measured locally, with a subsequent study visit at Day 90. Doses of RASi, beta-blocker, and MRA were up-titrated in the HIC group to half optimal doses at randomization and to full optimal doses at Week 2, if measures including NT-proBNP change, indicated it was safe to do so. In patients with >10% increase in NT-proBNP relative to the pre-discharge level, the protocol stated that physicians should consider increasing loop diuretic doses and not up-titrating beta-blockers. Up-titration could be delayed until safely indicated, with a safety visit 1 week after any delayed up-titration. Patients in the UC group were followed up according to local practice until a study visit performed at Day 90 after randomization. All randomized patients were contacted at Day 180 to assess the occurrence of rehospitalizations and death.

The primary endpoint was the composite of all-cause death or first HF rehospitalization at Day 180. Secondary endpoints included 180-day all-cause death and change in EQ-5D visual analogue scale (VAS) from baseline to Day 90.[7]

The study was approved by appropriate competent authorities and all sites obtained approval from the ethics committees. All patients provided written informed consent. The study is registered at ClinicalTrials.gov, NCT03412201.

## Stratifications and definitions

In the overall STRONG-HF population, baseline characteristics and outcomes are presented across tertiles of baseline NT-proBNP. Baseline NT-proBNP concentrations were those measured at the time of randomization. A further stratification based on randomization arm was used to show the interaction between baseline NT-proBNP and treatment strategy in improving outcomes. NT-proBNP was evaluated at all study visits in the HIC group and only at 90-day study visit in the UC group. Thus, only in the HIC group, further NT-proBNP changes were evaluated from baseline (i.e. within 2 days prior to discharge or Study Visit 2) to 1 week after randomization (i.e. Study Visit 3). Patients were grouped according to changes in NT-proBNP as decreased, stable and increased defined as a ≥ 30% decrease, a <30% decrease to ≤10% increase, ; and a >10% increase, respectively.[8–10]

## Statistical analysis

Continuous variables are presented as mean (standard deviation), median (25th, 75th percentiles), or as adjusted mean and associated standard error, and categorical variables as number and percentage. Comparisons of baseline characteristics among groups defined by NT-proBNP tertiles and NT-proBNP changes were performed by means of Jonckheere–Terpstra trend test for continuous variables, Cochran–Armitage trend test for binary variables, Cochran–Mantel–Haenszel general association for categorical variables, and Cochran–Mantel–Haenszel non-zero correlation for ordinal variables. Comparisons between groups regarding changes in vital signs and laboratory measures were assessed by analysis of covariance (ANCOVA) models adjusted for baseline value.

Primary and secondary endpoints through 180 days were restricted to patients enrolled at sites where the ethics committee approved the amended protocol allowing follow-up of patients through Day 180, and in the cohort of patients enrolled before the primary endpoint was changed from 90 to 180 days the results were down-weighted proportional to half its sample size. Cox proportional hazards regression analysis was performed to evaluate the impact of baseline NT-proBNP and NT-proBNP change on the study endpoints, using a landmark approach for the latter grouping.[11] The treatment effect of HIC vs. UC on the primary endpoint was modelled as a function of continuous baseline NT-proBNP, as a restricted cubic spline with three knots. NT-proBNP was log-transformed for analysis. Results are described as hazard ratio (HR) and 95% confidence interval (CI). Kaplan–Meier curves stratified by baseline NT-proBNP tertiles and NT-proBNP changes at Week 1 are also reported. Because the relative hazards among the NT-proBNP change groups differed over time, cumulative risks at 30, 60, and 90 days are provided, with NT-change groups compared using *z*-tests constructed from the Kaplan–Meier estimates and their associated standard errors. Proportional odds models were used to assess independent predictors of NT-proBNP changes; results are reported as odds ratio (OR) and associated 95% CIs. Covariates were selected using backwards selection with $P < 0.10$ across 10 multiple imputation datasets as the criterion for staying. The imputation model included the outcome and the baseline covariates, and used a Markov chain Monte Carlo method that assumes multivariate normality. The potential modification of the treatment effect on EQ-5D VAS by baseline NT-proBNP was assessed using ANCOVA with adjustment for baseline EQ-VAS and randomization stratification factors (LVEF ≤40/>40% and geographic region). Analyses were restricted to countries where a linguistically validated translation was available (i.e. excludes subjects from Mozambique).

The average dose of the three medications (RAS modulator, beta-blocker, and MRA) relative to the optimal doses (see Supplementary data online, *Table S3* in the primary publication)[6] were computed for each patient. The trajectory of this average percentage optimal dose over time is presented for the categorized 1-week NT-proBNP changes.

Two-sided *P*-values <0.05 were considered to be statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

# Results

## Baseline *N*-terminal pro-B-type natriuretic peptide

Baseline NT-proBNP plasma concentrations were available for all the 1078 patients enrolled except 1 patient who was randomized shortly after the site was closed due to operational issues. Thus, 1077 out of the 1078 patients randomized were analysed and divided according to tertiles of baseline NT-proBNP levels into those with <2159, 2160–4165, and ≥4165 ng/L plasma concentrations. As shown in *Table 1*, patients with higher NT-proBNP concentrations at baseline were older, more likely to have history of atrial fibrillation or flutter or of acute coronary syndrome and had a lower LVEF, when compared with those with lower NT-proBNP concentrations. Patients with the higher NT-proBNP concentrations also had higher serum creatinine and bilirubin and lower haemoglobin and cholesterol levels and were treated with higher diuretic doses. Guideline-recommended medical therapy GRMT was administered equally at randomization among the different baseline NT-proBNP tertiles.

A total of 1007 patients were randomized at sites that followed patients through Day 180 and had baseline NT-proBNP values available. Patients with higher NT-proBNP concentrations at baseline had worse outcomes (*Figure 1* and Supplementary data online, *Figure S1*). However, the beneficial effects of HIC vs. UC were independent of baseline NT-proBNP values both when patients were divided based on NT-proBNP tertiles (interaction $P = 0.1965$) and when NT-proBNP was evaluated as a continuous variable (interaction $P = 0.3204$; *Table 2*, *Figures 1* and *2*, Supplementary data online, *Figure S1*), and remained independent after covariate adjustment (adjusted interaction $P = 0.2444$ and 0.4245, respectively). A large reduction in the primary endpoint occurred in patients in the upper tertile of baseline NT-proBNP concentrations levels randomized to HIC as they showed a similar outcome as that of patients in the lower tertiles (*Figure 1*). Similar results were observed for the secondary endpoint 180-day all-cause mortality (see Supplementary data online, *Figures S1 and S2*).

With respect of the impact of atrial fibrillation or flutter on NT-proBNP plasma concentrations and their relation with the effects of treatment, results of a pre-specified subgroup analysis already showed that the treatment effect on the primary outcome (180-day HF readmission or death) did not differ significantly between patients with and without a history or presence of atrial fibrillation or flutter at screening (risk difference 6.1% vs. 9.8%, interaction $P = 0.50$).[6] We then examined whether the treatment effect varied as a function of baseline NT-proBNP as a continuous variable separately among patients with and without a history or presence of atrial fibrillation or flutter at screening. Although plots of the treatment effect by continuous baseline NT-proBNP suggest less of a benefit of HIC in patients with atrial fibrillation or flutter and low baseline NT-proBNP, the treatment-by-NT-proBNP interaction was not statistically significant in either group ($P = 0.8415$ in patients without and $P = 0.2236$ in patients with atrial fibrillation or flutter; see Supplementary data online, *Figure S3*).

A tendency to larger improvements in EQ-5D VAS scores from randomization to Day 90 in the HIC group than in UC were observed in the upper baseline NT-proBNP tertiles with, however, no significant interaction (interaction $P = 0.92$; *Table 2*).

## Changes in *N*-terminal pro-B-type natriuretic peptide in the high intensity care group

Assessment of the change from pre-discharge to 1 week post-discharge of NT-proBNP concentrations in the HIC group showed a decrease (≥30%) in 149 patients (30%), stable values (between <30% decrease and ≤10% increase) in 212 (43%) and an increase (>10%) in 135 patients (27%). At 3 weeks post-discharge, 230 (48%), 123 (26%) and 123 (26%) patients had decreased, stable and increased NT-proBNP levels from randomization values, respectively. The proportion of patients with a NT-proBNP decrease relative to pre-discharge values increased throughout the following visits, though with meaningful changes at each visit during follow-up (see Supplementary data online, *Figure S4*).

With respect of the relation between baseline variables and changes in NT-proBNP concentrations at Week 1 after discharge, patients with stable or increased NT-proBNP levels were older, more frequently males and Caucasian, and more likely to have low blood pressure, history of atrial fibrillation or flutter, ischaemic aetiology of HF, chronic obstructive pulmonary disease and more severe symptoms (NYHA Class IV) when compared with those with decreased NT-proBNP concentrations. With respect to laboratory measurements, these patients also had higher urea and bilirubin concentrations and lower cholesterol concentrations (see Supplementary data online, *Table S1*). Predictors of NT-proBNP increase at 1 week after discharge are reported at Supplementary data online, *Table S2*.

Compared with patients with a decrease, those with an increase in NT-proBNP values at Week 1 had concomitant worsening in renal and liver function with a decrease in estimated glomerular filtration rate eGFR of −5.99 (95% CI −8.49, −3.49) mL/min/1.73 $m^2$ and an increase in alanine aminotransferase of 11.32 (95% CI 6.41, 16.23) U/L (see Supplementary data online, *Table S3*).

Guideline-recommended medical therapy administration at randomization was similar across the groups defined by NT-proBNP changes occurring at Week 1, except for MRA that were more frequently administered in patients with subsequent decreased NT-proBNP levels (*Table 3*). At Week 2 after randomization, patients with a NT-proBNP decrease received the highest doses of GRMT, followed by those with stable NT-proBNP and with the least therapy given to those who had a NT-proBNP increase (88.6%, 81.8%, and 70.4% of GRMT target doses, respectively). Similarly, there was a gradation in the use of diuretics with those with NT-proBNP decrease receiving the lowest doses of diuretics followed by those with stable NT-proBNP and with the highest doses of loop diuretics administered to those with a NT-proBNP increase. Thus, patients with a NT-proBNP increase at Week 1 were less likely to receive >50% target doses of ACEi/ARB/ARNI, beta-blocker, and MRA and were on higher doses of loop diuretics (see Supplementary data online, *Table S3*). These differences were most pronounced during the first weeks after discharge and then became smaller. However, with these medication adjustments, patients with decreased, stable, and increased NT-proBNP at Week 1 achieved an average of 82.2%, 80.1%, and

**Table 1 Baseline characteristics according to baseline *N*-terminal pro-B-type natriuretic peptide tertiles**

| | Tertile 1 < 2159 ng/L (*n* = 359) | Tertile 2 2160–4165 ng/L (*n* = 359) | Tertile 3 ≥ 4165 ng/L (*n* = 359) | *P*-value for trend |
|---|---|---|---|---|
| Age, years | 61.7 (13.85) | 62.4 (13.47) | 64.7 (13.29) | 0.0018 |
| Male sex | 220 (61.3%) | 220 (61.3%) | 221 (61.6%) | 0.9694 |
| Race | | | | |
| Black | 82 (22.8%) | 78 (21.7%) | 70 (19.6%) | 0.6769 |
| Caucasian | 272 (75.8%) | 276 (76.9%) | 284 (79.3%) | |
| Systolic blood pressure, mmHg | 124.0 (12.40) | 122.7 (13.28) | 121.9 (13.08) | 0.0839 |
| History of atrial fibrillation or atrial flutter or present at screening | 145 (40.4%) | 160 (44.6%) | 177 (49.3%) | 0.0163 |
| *Medical history* | | | | |
| Stroke or transient ischaemic attack | 28 (7.8%) | 36 (10.1%) | 35 (9.8%) | 0.3597 |
| Malignancies | 10 (2.8%) | 8 (2.2%) | 11 (3.1%) | 0.8176 |
| Diabetes | 103 (28.7%) | 105 (29.4%) | 105 (29.3%) | 0.8506 |
| Acute coronary syndrome | 90 (25.1%) | 104 (29.0%) | 117 (32.6%) | 0.0262 |
| Coronary artery bypass surgery | 14 (3.9%) | 23 (6.4%) | 22 (6.1%) | 0.1864 |
| Percutaneous transluminal coronary intervention | 48 (13.4%) | 52 (14.5%) | 52 (14.5%) | 0.6570 |
| Moderate or severe chronic obstructive pulmonary disease or asthma | 5 (1.4%) | 12 (3.3%) | 10 (2.8%) | 0.2839 |
| Cardiac resynchronization therapy | 1 (0.3%) | 0 | 5 (1.4%) | 0.0761 |
| Automatic internal cardiac defibrillator | 0 | 4 (1.1%) | 5 (1.4%) | 0.0625 |
| *Heart failure history* | | | | |
| History of heart failure | 304 (84.7%) | 311 (86.6%) | 301 (83.8%) | 0.7535 |
| NYHA Class 1 month before hospital admission | | | | |
| I | 18 (5.4%) | 15 (4.5%) | 30 (8.9%) | 0.3919 |
| II | 116 (34.9%) | 115 (34.6%) | 76 (22.6%) | |
| III | 120 (36.1%) | 145 (43.7%) | 150 (44.6%) | |
| IV | 78 (23.5%) | 57 (17.2%) | 80 (23.8%) | |
| Ischaemic aetiology | 154 (43.0%) | 176 (49.0%) | 184 (51.4%) | 0.0248 |
| Left ventricular ejection fraction, % | 38.0 (12.15) | 36.9 (12.78) | 34.0 (12.31) | <0.0001 |
| Hospitalized for heart failure in the past year | 84 (23.4%) | 86 (24.0%) | 103 (28.7%) | 0.1031 |
| Number of heart failure hospitalizations in the past year per patient | 0.3 (0.55) | 0.4 (1.68) | 0.4 (0.76) | 0.2773 |
| History of atrial fibrillation or atrial flutter | 148 (41.2%) | 167 (46.5%) | 181 (50.4%) | 0.0135 |
| Type of atrial fibrillation or atrial flutter | | | | |
| Paroxysmal | 31 (20.8%) | 45 (27.6%) | 41 (23.0%) | 0.4831 |
| Permanent | 90 (60.4%) | 97 (59.5%) | 106 (59.6%) | |
| Persistent | 28 (18.8%) | 21 (12.9%) | 31 (17.4%) | |
| *Laboratory data* | | | | |
| Haemoglobin, g/L | 139.0 (128.0, 154.0) | 135.0 (121.0, 147.0) | 135.0 (122.0, 148.0) | 0.0002 |
| Lymphocytes, % | 29.4 (22.9, 36.0) | 27.0 (20.3, 33.8) | 24.6 (17.7, 31.3) | <0.0001 |

*Continued*

**Table 1** ***Continued***

| | Tertile 1 < 2159 ng/L (*n* = 359) | Tertile 2 2160–4165 ng/L (*n* = 359) | Tertile 3 ≥ 4165 ng/L (*n* = 359) | *P*-value for trend |
|---|---|---|---|---|
| White blood cells, $10^9$/L | 6.8 (5.7, 7.8) | 6.9 (5.5, 8.3) | 6.8 (5.6, 8.2) | 0.5221 |
| Glucose, mmol/L | 5.4 (4.8, 7.2) | 5.5 (5.0, 6.5) | 5.6 (4.9, 6.8) | 0.3790 |
| Creatinine, μmol/L | 98.6 (84.0, 113.0) | 104.0 (88.0, 121.0) | 107.8 (89.0, 128.0) | <0.0001 |
| Potassium, mmol/L | 4.2 (3.9, 4.6) | 4.4 (4.0, 4.6) | 4.3 (3.9, 4.6) | 0.8716 |
| Sodium, mmol/L | 141.0 (138.0, 143.7) | 140.0 (137.4, 143.0) | 140.0 (137.1, 143.0) | 0.0851 |
| Urea, mmol/L | 6.9 (5.8, 8.8) | 7.1 (6.0, 9.1) | 7.9 (6.1, 10.0) | 0.0001 |
| ALT, U/l | 20.0 (15.3, 31.6) | 21.1 (15.3, 32.0) | 22.0 (14.4, 33.0) | 0.8572 |
| Total bilirubin, μmol/L | 13.0 (10.2, 18.8) | 13.4 (10.6, 20.3) | 14.6 (10.0, 23.9) | 0.0152 |
| Total cholesterol, mmol/L | 4.2 (3.7, 4.9) | 4.2 (3.4, 5.0) | 4.0 (3.2, 4.7) | <0.0001 |
| *Oral heart failure medications taken pre-randomization* | | | | |
| ACE inhibitors/ARBs/ARNI | 104 (69.8%) | 139 (65.9%) | 83 (61.5%) | 0.1402 |
| β-Blockers | 44 (29.5%) | 72 (34.1%) | 50 (37.0%) | 0.1786 |
| Mineralocorticoid receptor antagonists | 143 (96.0%) | 206 (97.6%) | 118 (87.4%) | 0.0028 |
| Loop diuretic | 143 (96.0%) | 204 (96.7%) | 128 (94.8%) | 0.6368 |

Values presented are *n* (%) for categorical variables and mean (SD) or median (25th, 75th percentiles) for continuous variables.

70.8% of GRMT doses at Day 90 and 80.3%, 78.9%, and 70.4% of optimal GRMT doses by Day 180, respectively (*Figure 3* and *Table 3*).

Landmark analyses excluded patients who experienced the event of interest before Week 1: 4 patients experienced the primary endpoint before Week 1, three of whom died. The rate of the primary endpoint at 60 and 90 days post-discharge differed between patients with decreased, stable and increased NT-proBNP at Week 1 with a rate of 8.3% vs. 2.2% at 60 days ($P = 0.039$) and of 11.1% vs. 4.0% at 90 days ($P = 0.045$) in patients with increased vs. those with decreased NT-proBNP concentrations at Week 1 (*Figure 4*). However, consistent with the decrease in the gap in GRMT titration over time, the rate of the primary endpoint at 180 days decreased and was similar across all the categories of NT-proBNP changes (13.5% in patients with a 1-week increase vs. 13.2% in those with a 1-week decrease; $P = 0.93$; *Figure 4*).

Cumulative rate of the secondary endpoint of all-cause death was similar in patients with increased, stable and decreased NT-proBNP at Week 1, up to 180 days (*Figure 5*). Change in NT-proBNP at Week 1, either unadjusted or adjusted by multivariable analysis, was not associated with the occurrence of the primary or secondary endpoints at 180 days (see Supplementary data online, *Table S4*).

# Discussion

We analysed the impact of NT-proBNP in STRONG-HF with two main purposes: first, to assess the associations of baseline NT-proBNP concentrations with the characteristics, outcomes, and treatment response of HIC vs. UC; and, second, to evaluate the impact of NT-proBNP changes at 1 week after randomization on the subsequent treatment and outcomes of patients in the HIC arm. Our analysis confirms that NT-proBNP concentrations before discharge are associated with more severe HF, more comorbidities, such as atrial fibrillation or flutter, and poorer outcome. However, the beneficial effects of HIC vs. UC were similar regardless of baseline NT-proBNP and tended to be larger in patients in the upper tertile of baseline NT-proBNP concentrations. At 1 week, a ≥ 30% decrease in NT-proBNP concentrations after discharge occurred in 149 (30%) patients, and a ≥ 10% increase in NT-proBNP in 139 patients. Compared with patients with a decrease in NT-proBNP at 1 week, patients with an increase from baseline in NT-proBNP concentrations were less likely to receive >50% target doses of ACEi/ARB/ARNI, beta-blocker and MRA and received higher doses of loop diuretics. These differences were most pronounced during the first weeks after discharge and then became smaller. Following these medication adjustments, patients with decreased, stable, and increased NT-proBNP at Week 1 after discharge achieved an average of 84.9%, 82.4%, and 72.3% of target GRMT doses at Day 90 and 80.7%, 78.9%, and 70.6% of target GRMT doses by Day 180, respectively. The rate of the primary endpoint at 60 and 90 days after discharge differed between patients with decreased, stable and increased NT-proBNP at Week 1, with outcomes being the worst in those with a NT-proBNP increase. However, these outcomes became similar across all the categories of NT-proBNP changes at 180 days (*Structured Graphical Abstract*).

The relation between baseline NT-proBNP concentrations and the effect of HF medications on clinical outcomes has been studied mostly in patients with chronic HF yielding variable results depending on patient characteristics and the medication tested.[12–17] In patients hospitalized for HF, administration of sacubitril–valsartan led to a greater reduction in NT-proBNP concentrations than enalapril regardless of baseline NT-proBNP in PIONEER-HF. However, no data are reported about the interaction between baseline NT-proBNP and the effects of sacubitril–valsartan on cardiovascular death or HF hospitalization.[18] In

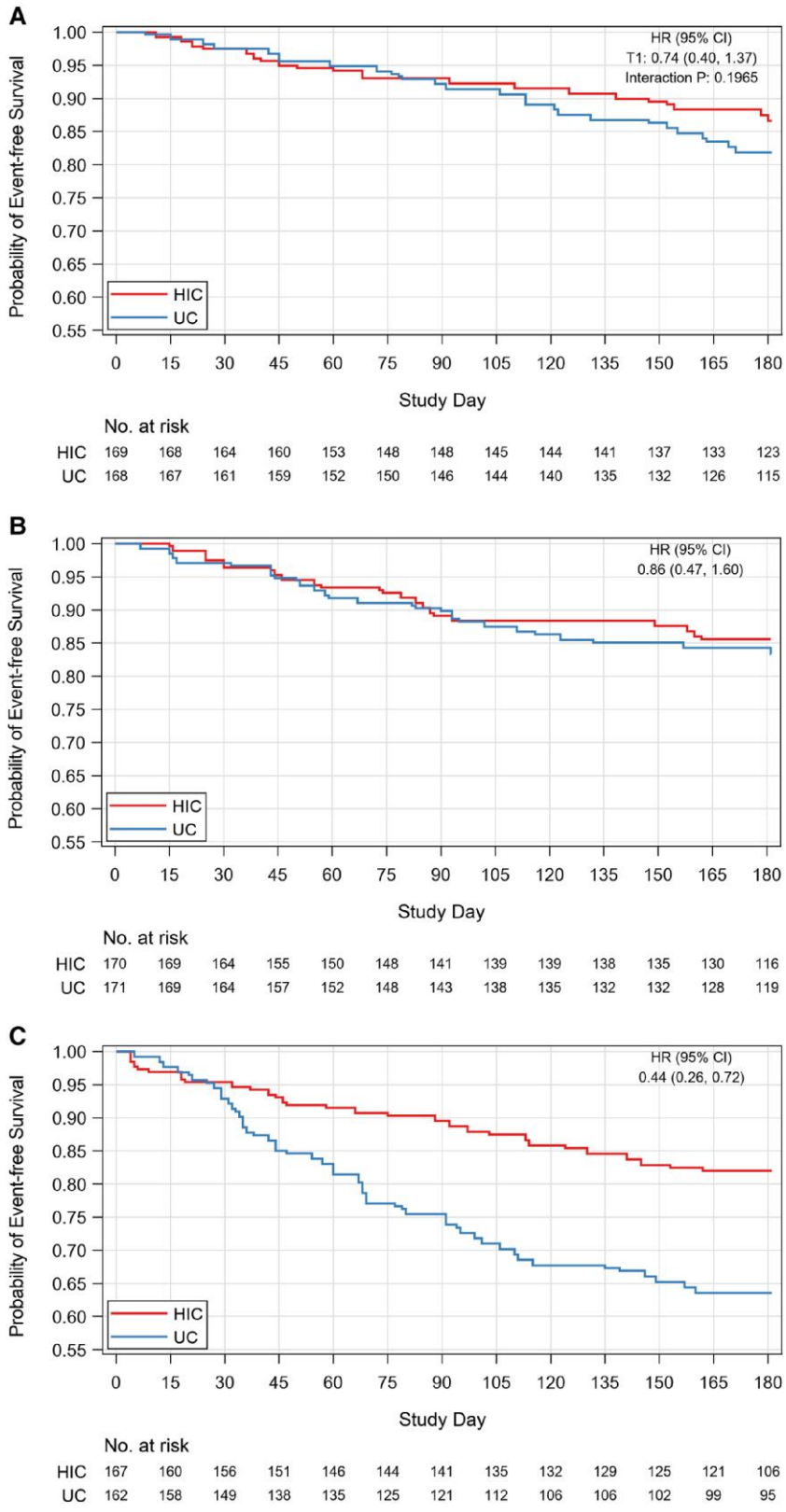



**Figure 1** Unadjusted Kaplan–Meier curves for the primary endpoint by baseline *N*-terminal pro-B-type natriuretic peptide and treatment strategy: (*A*) first tertile, (*B*) second tertile, (*C*) third tertile. The figure shows Kaplan–Meier estimates of cumulative event-free survival for the composite of all-cause mortality or heart failure rehospitalization according to the high intensity care or usual care strategy in the tertiles of baseline *N*-terminal pro-B-type natriuretic peptide.

**Table 2 Outcomes according to baseline *N*-terminal pro-B-type natriuretic peptide tertiles and treatment strategy**

| Endpoint | High intensity care | Usual care | Unadjusted treatment effect | | Adjusted treatment effect | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P*-value[a] | HR (95% CI) | *P*-value[a] |
| *Primary endpoint* | *n/N* (KM%) | *n/N* (KM%) | | | | |
| All-cause death or heart failure readmission by Day 180[b] | 74/506 (23.5%) | 109/502 (15.2%) | 0.62 (0.45, 0.86) | 0.0043 | 0.61 (0.44, 0.85) | 0.0032 |
| Tertile 1: NT-BNP <2160 | 21/169 (13.5%) | 27/168 (18.2%) | 0.74 (0.40, 1.37) | | 0.72 (0.39, 1.34) | |
| Tertile 2: NT-BNP 2160–4142 | 24/170 (14.4%) | 27/171 (16.7%) | 0.86 (0.47, 1.60) | | 0.85 (0.46, 1.57) | |
| Tertile 3: NT-BNP >4142 | 29/167 (18.0%) | 55/162 (36.5%) | 0.44 (0.26, 0.72) | | 0.45 (0.27, 0.74) | |
| Treatment-by-tertile interaction | | | | 0.1965 | | 0.2444 |
| *Secondary endpoints* | | | | | | |
| All-cause death by Day 180[c] | 39/506 (8.6%) | 48/502 (10.1%) | 0.83 (0.52, 1.32) | 0.4342 | 0.78 (0.49, 1.25) | 0.3098 |
| Tertile 1: NT-BNP <2160 | 10/169 (6.6%) | 8/168 (4.9%) | 1.30 (0.47, 3.62) | | 1.40 (0.50, 3.92) | |
| Tertile 2: NT-BNP 2160–4142 | 9/170 (6.1%) | 12/171 (6.9%) | 0.87 (0.33, 2.25) | | 0.86 (0.33, 2.24) | |
| Tertile 3: NT-BNP >4142 | 20/167 (13.2%) | 28/162 (19.1%) | 0.68 (0.36, 1.28) | | 0.59 (0.31, 1.13) | |
| Treatment-by-tertile interaction | | | | 0.5673 | | 0.3658 |
| | **LS: mean (SE)** | | **Mean difference (95% CI)** | ***P*-value** | **Mean difference (95% CI)** | ***P*-value** |
| Change from baseline to Day 90 in EQ-5D VAS[d] | 10.7 (0.88) | 7.2 (0.90) | 3.49 (1.74, 5.24) | <0.0001 | 3.74 (2.06, 5.43) | <0.0001 |
| Tertile 1: NT-BNP <2160 | 12.5 (1.24) | 9.4 (1.20) | 3.04 (0.11, 5.97) | | 2.62 (−0.23, 5.47) | |
| Tertile 2: NT-BNP 2160–4142 | 10.7 (1.20) | 7.0 (1.28) | 3.70 (0.74, 6.65) | | 4.04 (1.16, 6.91) | |
| Tertile 3: NT-BNP >4142 | 8.5 (1.30) | 4.7 (1.32) | 3.87 (0.70, 7.04) | | 4.64 (1.55, 7.73) | |
| Treatment-by-tertile interaction | | | | 0.9209 | | 0.6183 |

Results restricted to subjects at sites where patients were followed to 180 days. Results for patients in Cohort 1 are down-weighted proportional to half its sample size. *n/N* (Kaplan–Meier estimates) are presented. Hazard ratios from Cox proportional hazards model.
[a]Treatment-by-tertile interaction *P*-value or overall main effect *P*-value presented.
[b]Adjusted for baseline diastolic blood pressure, baseline NT-proBNP, ischaemic aetiology, and oedema.
[c]Adjusted for baseline creatinine, baseline haemoglobin, baseline urea, and baseline NT-proBNP.
[d]All analyses adjusted for baseline EQ-VAS, region, and LVEF group (≤40/>40) using ANCOVA. Additional adjustment for baseline haemoglobin, baseline creatinine, baseline cholesterol, baseline NT-proBNP, hospitalized for heart failure in prior year, oedema, and NYHA classification.

EMPULSE, baseline NT-proBNP levels had no relation with the effect of empagliflozin vs. placebo on the primary endpoint.[19] Our analysis shows that the HIC strategy including rapid up-titration of ACEi/ARB/ARNI, beta-blocker, and MRA, and frequent follow-up visits after an HF hospitalization, was associated with a better outcome regardless of initial NT-proBNP concentrations, compared with UC. Although numerically larger effects of HIC vs. UC were observed in patients with higher NT-proBNP concentrations at the time of randomization (*Figures 1* and *2*), these patients are those at higher risk, and therefore they also had the larger benefit from GRMT. Altogether with the early beneficial effects on outcome of GRMT, these data emphasize the need for early and rapid initiation and up-titration of GRMT in these high-risk patients.[20–23]

We assessed the impact of the changes in NT-proBNP at 1 week after randomization on up-titration of GRMT in the HIC arm and on outcomes. For the purpose of this analysis, patients were divided into three groups based on their NT-proBNP change from baseline to 1 week after discharge. Cut-off values were chosen based on the study protocol and data from the literature. Namely, an increase in NT-proBNP levels was defined as a >10% change as this was the cut-off value that mandated changes in medical therapy according to our study protocol.[4,6] A 30% cut-off was chosen to define a meaningful decrease from baseline according to previous data showing its association with a favourable outcome in patients with acute HF.[8–10,24,25]

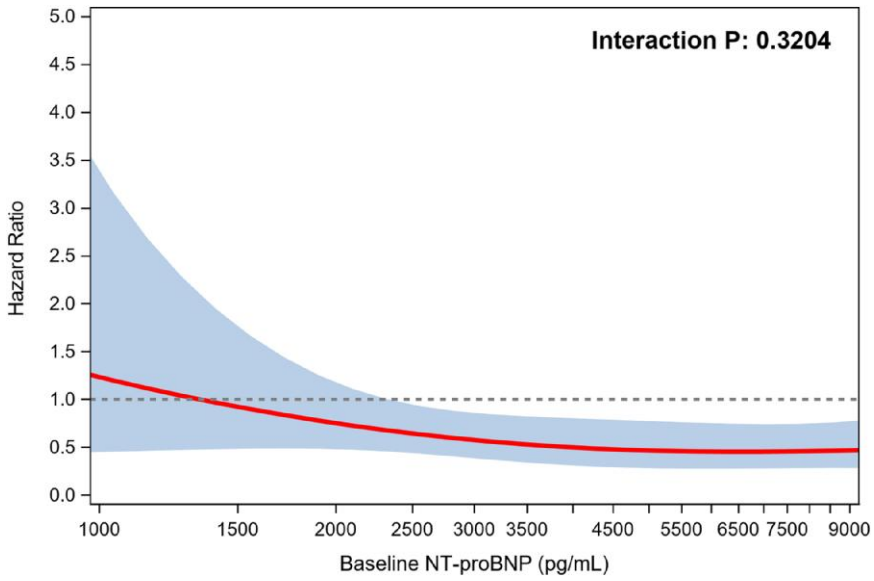



**Figure 2** Treatment effect of high intensity care vs. usual care on the primary endpoint of death or HF readmission through Day 180 according to baseline *N*-terminal pro-B-type natriuretic peptide. The figure shows the hazard ratio estimated from a Cox proportional hazards model for the effect of high intensity care vs. usual care on the composite of all-cause mortality or heart failure rehospitalization at Day 180 (primary endpoint) according to baseline *N*-terminal pro-B-type natriuretic peptide.

**Table 3 Oral heart failure medications relative to optimal doses by *N*-terminal pro-B-type natriuretic peptide change categories at 1 week**

| | Patients with decrease in NT-proBNP ($n = 149$) | Patients with stable NT-proBNP ($n = 212$) | Patients with increase in NT-proBNP ($n = 135$) | *P*-value for trend |
|---|---|---|---|---|
| *Oral heart failure medications optimal dose categories at Visit 2: post-rand* | | | | |
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 2 (1.3%) | 3 (1.4%) | 2 (1.5%) | 0.6052 |
| <1/2 Optimal dose | 27 (18.1%) | 49 (23.1%) | 20 (14.8%) | |
| 1/2–<Full optimal dose | 119 (79.9%) | 153 (72.2%) | 112 (83.0%) | |
| ≥Full optimal dose | 1 (0.7%) | 7 (3.3%) | 1 (0.7%) | |
| β-Blockers | | | | |
| None | 4 (2.7%) | 5 (2.4%) | 1 (0.7%) | 0.2270 |
| <1/2 Optimal dose | 15 (10.1%) | 34 (16.0%) | 11 (8.1%) | |
| 1/2–<Full optimal dose | 129 (86.6%) | 170 (80.2%) | 121 (89.6%) | |
| ≥Full optimal dose | 1 (0.7%) | 3 (1.4%) | 2 (1.5%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 0 | 2 (0.9%) | 6 (4.4%) | <0.0001 |
| <1/2 Optimal dose | 0 | 1 (0.5%) | 0 | |
| 1/2–<Full optimal dose | 72 (48.3%) | 139 (65.6%) | 83 (61.5%) | |
| ≥Full optimal dose | 77 (51.7%) | 70 (33.0%) | 46 (34.1%) | |
| | 59.1 (39.71) | 64.1 (48.02) | 58.3 (57.35) | 0.1677 |

*Continued*

**Table 3** ***Continued***

| | Patients with decrease in NT-proBNP ($n = 149$) | Patients with stable NT-proBNP ($n = 212$) | Patients with increase in NT-proBNP ($n = 135$) | *P*-value for trend |
|---|---|---|---|---|
| Loop diuretic dose, furosemide equivalence | | | | |
| *Oral heart failure medications optimal dose categories at Visit 3: Week 1* | | | | |
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 1 (0.7%) | 2 (0.9%) | 3 (2.2%) | 0.7511 |
| <1/2 Optimal dose | 26 (17.4%) | 47 (22.2%) | 22 (16.3%) | |
| 1/2–<Full optimal dose | 120 (80.5%) | 152 (71.7%) | 108 (80.0%) | |
| ≥Full optimal dose | 2 (1.3%) | 11 (5.2%) | 2 (1.5%) | |
| β-Blockers | | | | |
| None | 2 (1.3%) | 4 (1.9%) | 8 (5.9%) | 0.0382 |
| <1/2 Optimal dose | 16 (10.7%) | 38 (17.9%) | 17 (12.6%) | |
| 1/2–<Full optimal dose | 127 (85.2%) | 164 (77.4%) | 108 (80.0%) | |
| ≥Full optimal dose | 4 (2.7%) | 6 (2.8%) | 2 (1.5%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 1 (0.7%) | 3 (1.4%) | 11 (8.1%) | <0.0001 |
| <1/2 Optimal dose | 0 | 2 (0.9%) | 0 | |
| 1/2–<Full optimal dose | 70 (47.0%) | 125 (59.0%) | 83 (61.5%) | |
| ≥Full optimal dose | 78 (52.3%) | 82 (38.7%) | 41 (30.4%) | |
| Loop diuretic dose, furosemide equivalence | 48.3 (33.91) | 59.7 (45.71) | 69.6 (58.42) | <0.0001 |
| *Oral heart failure medications optimal dose categories at Visit 4: Week 2* | | | | |
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 1 (0.7%) | 2 (0.9%) | 3 (2.3%) | <0.0001 |
| <1/2 Optimal dose | 11 (7.5%) | 24 (11.3%) | 14 (10.6%) | |
| 1/2–<Full optimal dose | 24 (16.4%) | 57 (26.9%) | 55 (41.7%) | |
| ≥Full optimal dose | 110 (75.3%) | 129 (60.8%) | 60 (45.5%) | |
| βBlockers | | | | |
| None | 2 (1.4%) | 3 (1.4%) | 11 (8.3%) | <0.0001 |
| <1/2 Optimal dose | 15 (10.3%) | 23 (10.8%) | 10 (7.6%) | |
| 1/2–<Full optimal dose | 25 (17.1%) | 78 (36.8%) | 70 (53.0%) | |
| ≥Full optimal dose | 104 (71.2%) | 108 (50.9%) | 41 (31.1%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 1 (0.7%) | 4 (1.9%) | 12 (9.1%) | <0.0001 |
| <1/2 Optimal dose | 0 | 1 (0.5%) | 0 | |
| 1/2–<Full optimal dose | 3 (2.1%) | 26 (12.3%) | 28 (21.2%) | |
| ≥Full optimal dose | 142 (97.3%) | 181 (85.4%) | 92 (69.7%) | |
| Loop diuretic dose, furosemide equivalence | 42.9 (34.42) | 59.2 (41.40) | 70.9 (63.96) | <0.0001 |
| *Oral heart failure medications optimal dose categories at Visit 5: Week 3* | | | | |

*Continued*

**Table 3** ***Continued***

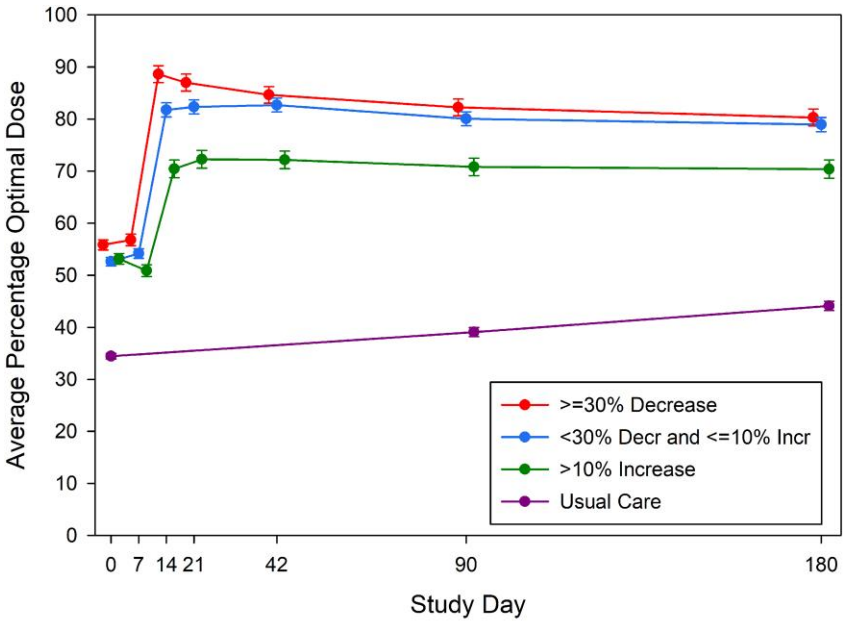
| | Patients with decrease in NT-proBNP ($n = 149$) | Patients with stable NT-proBNP ($n = 212$) | Patients with increase in NT-proBNP ($n = 135$) | *P*-value for trend |
|---|---|---|---|---|
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 1 (0.7%) | 2 (0.9%) | 3 (2.3%) | 0.0012 |
| <1/2 Optimal dose | 8 (5.5%) | 24 (11.4%) | 16 (12.3%) | |
| 1/2–<Full optimal dose | 36 (24.8%) | 56 (26.5%) | 45 (34.6%) | |
| ≥Full optimal dose | 100 (69.0%) | 129 (61.1%) | 66 (50.8%) | |
| β-Blockers | | | | |
| None | 2 (1.4%) | 4 (1.9%) | 11 (8.5%) | <0.0001 |
| <1/2 Optimal dose | 15 (10.3%) | 24 (11.4%) | 17 (13.1%) | |
| 1/2–<Full optimal dose | 32 (22.1%) | 69 (32.7%) | 56 (43.1%) | |
| ≥Full optimal dose | 96 (66.2%) | 114 (54.0%) | 46 (35.4%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 1 (0.7%) | 6 (2.8%) | 12 (9.2%) | <0.0001 |
| <1/2 Optimal dose | 0 | 1 (0.5%) | 0 | |
| 1/2–<Full optimal dose | 4 (2.8%) | 21 (10.0%) | 21 (16.2%) | |
| ≥Full optimal dose | 140 (96.6%) | 183 (86.7%) | 97 (74.6%) | |
| Loop diuretic dose, furosemide equivalence | 43.7 (38.00) | 58.5 (42.08) | 78.7 (100.11) | <0.0001 |
| *Oral heart failure medications optimal dose categories at Visit 6: Week 6* | | | | |
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 0 | 1 (0.5%) | 2 (1.6%) | 0.0030 |
| <1/2 Optimal dose | 8 (5.8%) | 24 (11.7%) | 17 (13.4%) | |
| 1/2–<Full optimal dose | 39 (28.1%) | 53 (25.9%) | 43 (33.9%) | |
| ≥Full optimal dose | 92 (66.2%) | 127 (62.0%) | 65 (51.2%) | |
| β-Blockers | | | | |
| None | 3 (2.2%) | 4 (2.0%) | 13 (10.2%) | <0.0001 |
| <1/2 Optimal dose | 13 (9.4%) | 26 (12.7%) | 17 (13.4%) | |
| 1/2–<Full optimal dose | 40 (28.8%) | 61 (29.8%) | 48 (37.8%) | |
| ≥Full optimal dose | 83 (59.7%) | 114 (55.6%) | 49 (38.6%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 3 (2.2%) | 7 (3.4%) | 14 (11.0%) | <0.0001 |
| 1/2–<Full optimal dose | 6 (4.3%) | 19 (9.3%) | 17 (13.4%) | |
| ≥Full optimal dose | 130 (93.5%) | 179 (87.3%) | 96 (75.6%) | |
| Loop diuretic dose, furosemide equivalence | 39.1 (35.17) | 59.8 (55.29) | 72.0 (60.20) | <0.0001 |
| *Oral heart failure medications optimal dose categories at Visit 7: Day 90* | | | | |
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 0 | 6 (2.9%) | 3 (2.3%) | 0.0053 |
| <1/2 Optimal dose | 11 (7.7%) | 27 (13.2%) | 19 (14.8%) | |

*Continued*

**Table 3** *Continued*

| | Patients with decrease in NT-proBNP ($n = 149$) | Patients with stable NT-proBNP ($n = 212$) | Patients with increase in NT-proBNP ($n = 135$) | *P*-value for trend |
|---|---|---|---|---|
| 1/2–<Full optimal dose | 43 (30.3%) | 53 (26.0%) | 45 (35.2%) | |
| ≥Full optimal dose | 88 (62.0%) | 118 (57.8%) | 61 (47.7%) | |
| β-Blockers | | | | |
| None | 5 (3.5%) | 7 (3.4%) | 11 (8.6%) | 0.0010 |
| <1/2 Optimal dose | 12 (8.5%) | 27 (13.2%) | 17 (13.3%) | |
| 1/2–<Full optimal dose | 45 (31.7%) | 61 (29.9%) | 53 (41.4%) | |
| ≥Full optimal dose | 80 (56.3%) | 109 (53.4%) | 47 (36.7%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 4 (2.8%) | 10 (4.9%) | 15 (11.7%) | 0.0002 |
| <1/2 Optimal dose | 0 | 0 | 1 (0.8%) | |
| 1/2–<Full optimal dose | 9 (6.3%) | 20 (9.8%) | 16 (12.5%) | |
| ≥Full optimal dose | 129 (90.8%) | 174 (85.3%) | 96 (75.0%) | |
| Loop diuretic dose, furosemide equivalence | 41.3 (39.96) | 51.0 (42.90) | 66.4 (53.06) | <0.0001 |
| *Oral heart failure medications optimal dose categories at Visit 8: Day 180* | | | | |
| ACE inhibitors/ARBs/ARNI | | | | |
| None | 0 | 4 (2.4%) | 5 (5.2%) | 0.0091 |
| <1/2 Optimal dose | 14 (12.4%) | 26 (15.9%) | 14 (14.4%) | |
| 1/2–<Full optimal dose | 30 (26.5%) | 48 (29.3%) | 35 (36.1%) | |
| ≥Full optimal dose | 69 (61.1%) | 86 (52.4%) | 43 (44.3%) | |
| β-Blockers | | | | |
| None | 3 (2.7%) | 5 (3.0%) | 8 (8.2%) | 0.0062 |
| <1/2 Optimal dose | 12 (10.6%) | 21 (12.8%) | 16 (16.5%) | |
| 1/2–<Full optimal dose | 42 (37.2%) | 57 (34.8%) | 40 (41.2%) | |
| ≥Full optimal dose | 56 (49.6%) | 81 (49.4%) | 33 (34.0%) | |
| Mineralocorticoid receptor antagonists | | | | |
| None | 3 (2.7%) | 5 (3.0%) | 7 (7.2%) | 0.0216 |
| <1/2 Optimal dose | 0 | 0 | 1 (1.0%) | |
| 1/2–<Full optimal dose | 6 (5.3%) | 9 (5.5%) | 10 (10.3%) | |
| ≥Full optimal dose | 104 (92.0%) | 150 (91.5%) | 79 (81.4%) | |
| Loop diuretic dose, furosemide equivalence | 34.8 (31.06) | 44.8 (37.13) | 65.8 (55.51) | <0.0001 |

Values presented are *n* (%) for categorical variables and mean (SD) for continuous variables.




| Group | V2: Day 0 | V3: Day 7 | V4: Day 14 | V5: Day 21 | V6: Day 42 | V7: Day 90 | V8: Day 180 |
|---|---|---|---|---|---|---|---|
| Usual Care | 34.5 (0.51) | --- | --- | --- | --- | 39.1 (0.87) | 44.1 (0.88) |
| >=30% Decrease | 55.8 (0.97) | 56.8 (1.09) | 88.6 (1.62) | 87.0 (1.62) | 84.6 (1.60) | 82.2 (1.61) | 80.3 (1.64) |
| <30% Decr. and <=10% Incr. | 52.6 (0.81) | 54.2 (0.91) | 81.8 (1.35) | 82.3 (1.34) | 82.7 (1.33) | 80.1 (1.34) | 78.9 (1.36) |
| >10% Increase | 53.2 (1.01) | 50.9 (1.14) | 70.4 (1.71) | 72.3 (1.70) | 72.2 (1.69) | 70.8 (1.70) | 70.4 (1.75) |

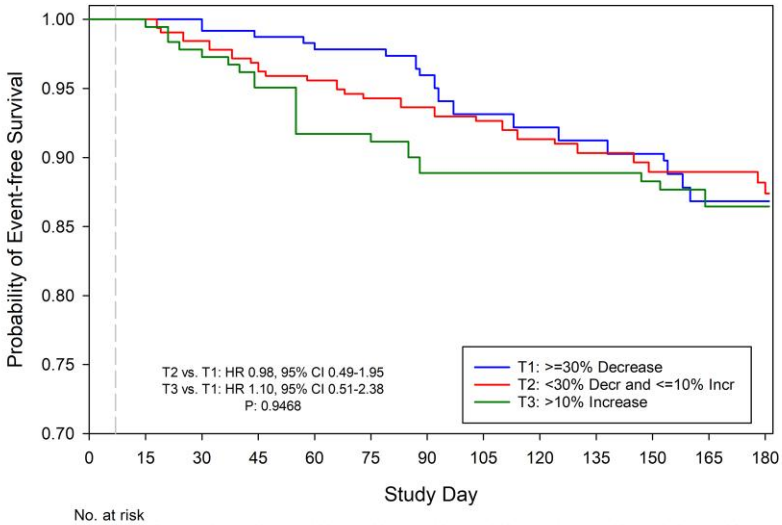
**Figure 3** Average percentage of optimal doses of GDMT by category of *N*-terminal pro-B-type natriuretic peptide change at Week 1 in the high intensity care arm and in the usual care arm. The figure shows the mean percentage of optimal doses of GDMT at different time points (baseline and follow-up visits in the usual care arm and in the high intensity care arm stratified by changes in *N*-terminal pro-B-type natriuretic peptide at Week 1.

According to the protocol of STRONG-HF, medical treatment was modified based on NT-proBNP changes with no titration of beta-blockers and an escalation of diuretic doses in patients who had an early increase from baseline in NT-proBNP concentrations. As a result, there was an early gradation of loop diuretic doses (more) and GRMT administration (less) in the early weeks after discharge in these patients. However, these differences became smaller and GRMT could be titrated, though to a lesser extent, also in patients with an early increase in NT-proBNP levels so that target doses were reached in 70% of these patients, i.e. a much larger proportion than in the UC group. Loop diuretic doses remained higher in those with stable NT-proBNP at Week 1, and even more so in those with an NT-proBNP increase, even at Day 180.

With regard to the prognostic significance of early changes in NT-proBNP after medical treatment, several studies reported an improvement of NT-proBNP levels after GRMT optimization and a possible association between NT-proBNP reduction and better clinical outcomes in both chronic[26–30] and acute settings.[8,16,31] Interestingly, consistent with the above mentioned studies, patients with an early increase of NT-proBNP concentrations had worse outcomes at 60 and 90 days but not at 180 days after randomization, compared with those with stable or decreased NT-proBNP plasma levels at Week 1. These results are consistent with the effects of delayed GRMT titration as well as with the time taken by GRMT to exert its beneficial effects. As the gap in GRMT doses between the decreased, stable, and increased NT-proBNP groups became smaller, the outcomes of the 3 groups became similar by 180 days. Our analysis suggest a new role for NT-proBNP measurements in the context of rapid up-titration of GRMT as they can alert the physician that the patient has persistent congestion and is not tolerating well rapid GRMT up-titration so that beta-blocker titration must be slowed or interrupted and/or higher diuretic doses must be administered. Such strategy was successful with a high proportion of high-risk patients reaching target doses of GRMT early after discharge and having a similar outcome compared with patients at lower risk.

## Limitations

Beyond the already described limitations of the overall STRONG-HF study,[6] there are some limitations that are specific to this analysis. First, subgroup analyses may have a limited statistical power in our study because of the limited sample size and number of events in the subgroups. Second, the analysis regarding the changes in NT-proBNP could be performed only in the HIC group since no information on NT-proBNP concentrations at early follow-up was available in the control arm. Thus, the association between NT-proBNP changes and treatment strategy on clinical outcomes could not be explored. Third, our results must be interpreted in the particular context of the trial both with respect to its inclusion criteria and follow-up strategy used in the HIC arm. To be enrolled in STRONG-HF patients had to show a decrease from admission in NT-proBNP concentrations with, however, values >1500 pg/mL before discharge and this criterion may have selected patients more likely to respond to treatment but still at high risk before discharge.

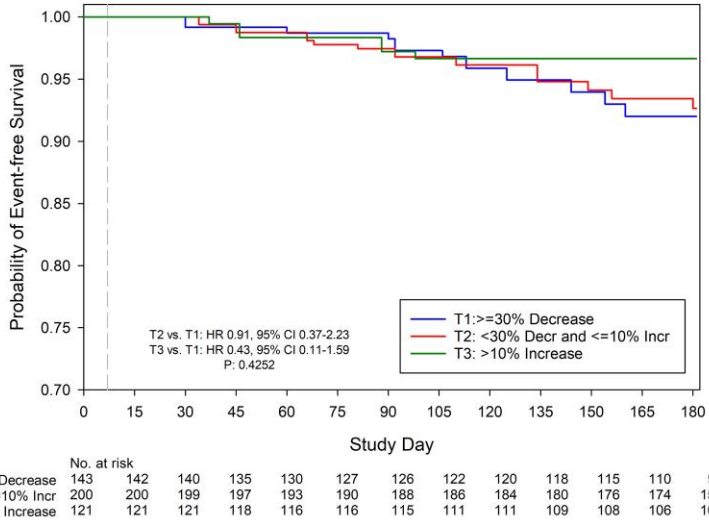



No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T1: >=30% Decrease | 143 | 142 | 140 | 134 | 128 | 125 | 121 | 116 | 115 | 113 | 110 | 103 | 87 |
| T2: <30% Decr and <=10% Incr | 200 | 200 | 196 | 192 | 186 | 182 | 180 | 177 | 174 | 171 | 166 | 165 | 148 |
| T3: >10% Increase | 120 | 120 | 117 | 111 | 107 | 107 | 104 | 101 | 101 | 99 | 97 | 92 | 89 |

| | Day 30 | | Day 60 | | Day 90 | | Day 180 | |
|---|---|---|---|---|---|---|---|---|
| | KM (%) | P-value | KM (%) | P-value | KM (%) | P-value | KM (%) | P-value |
| Patients with >=30% Decrease | 0.8 | [ref] | 2.2 | [ref] | 4.0 | [ref] | 13.2 | [ref] |
| Patients with <30% Decr to <=10% Incr | 1.6 | 0.5491 | 4.4 | 0.2624 | 6.4 | 0.3621 | 12.6 | 0.8872 |
| Patients with >10% Increase | 2.7 | 0.2833 | 8.3 | 0.0393 | 11.1 | 0.0453 | 13.5 | 0.9338 |

**Figure 4** Unadjusted Kaplan–Meier curves for the primary endpoint by change in *N*-terminal pro-B-type natriuretic peptide at Week 1 in the high intensity care arm. The figure shows Kaplan–Meier estimates of cumulative event-free survival for the composite of all-cause mortality or heart failure rehospitalization according to changes in *N*-terminal pro-B-type natriuretic peptide at Week 1 in the high intensity care arm. Landmark analyses at 30, 60, and 90 days are also reported.




No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T1: >=30% Decrease | 143 | 142 | 140 | 135 | 130 | 127 | 126 | 122 | 120 | 118 | 115 | 110 | 93 |
| T2: <30% Decr and <=10% Incr | 200 | 200 | 199 | 197 | 193 | 190 | 188 | 186 | 184 | 180 | 176 | 174 | 156 |
| T3: >10% Increase | 121 | 121 | 121 | 118 | 116 | 116 | 115 | 111 | 111 | 109 | 108 | 106 | 103 |

| | Day 30 | | Day 60 | | Day 90 | | Day 180 | |
|---|---|---|---|---|---|---|---|---|
| | KM (%) | P-value | KM (%) | P-value | KM (%) | P-value | KM (%) | P-value |
| Patients with >=30% Decrease | 0.8 | [ref] | 1.3 | [ref] | 1.8 | [ref] | 8.0 | [ref] |
| Patients with <30% Decr to <=10% Incr | 0.0 | 0.2931 | 1.3 | 0.9754 | 2.6 | 0.6317 | 7.4 | 0.8416 |
| Patients with >10% Increase | 0.0 | 0.2931 | 1.6 | 0.8253 | 2.8 | 0.6064 | 3.4 | 0.1287 |

**Figure 5** Unadjusted Kaplan–Meier curves for 180-day all-cause mortality by change in *N*-terminal pro-B-type natriuretic peptide at Week 1 in the high intensity care arm. The figure shows Kaplan–Meier estimates of cumulative event-free survival for the secondary endpoint of all-cause mortality according to changes in *N*-terminal pro-B-type natriuretic peptide at Week 1 in the high intensity care arm. Landmark analyses at 30, 60, and 90 days are also reported.

Lastly, sodium-glucose cotransporter 2 (SGLT2) inhibitors are now recommended as first-line therapy for patients with HF and their early initiation has beneficial effects also in patients with acute HF.[3,20] STRONG-HF was initiated prior this current evidence and recommendations for SGLT2 inhibitors. Thus, these drugs were not included in the study design.[4] However, it is likely that the benefits of HIC may extend also to SGLT2 inhibitors.

# Conclusions

Among patients with acute HF enrolled in the STRONG-HF trial, a rapid up-titration of oral HF medications before and early after discharge, performed under close follow-up and monitoring (i.e. HIC), is safe and effective in reducing HF rehospitalization or mortality regardless of baseline NT-proBNP. An early increase in NT-proBNP levels (>10%) 1 week after discharge was associated with a poorer outcome up to 90 days, but not at 180 days, in patients receiving HIC. This dichotomy was the result of investigators using NT-proBNP changes as an indicator that patients were not coping well with rapid GRMT implementation and treating them with more diuretics while slowing down GRMT up-titration. When this strategy was implemented, the benefits of HIC were similar irrespective of early post-discharge NT-proBNP changes, too.

# Supplementary data

Supplementary data is available at *European Heart Journal* online.

# Pre-registered clinical trial number

The pre-registered clinical trial number is NCT03412201.

# Ethical approval

The study was approved by appropriate competent authorities and all sites obtained approval from the ethics committees. All patients provided written informed consent.

# Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

# Conflict of interest

A.M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics, Bayer, and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. G.C. is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. .G.C. is director of Heart Initiative, a non-profit organization. B.D. is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. B.D. is director of Heart Initiative, a non-profit organization. A.C.S. has received honoraria for lectures or consultancy from AstraZeneca, Novartis, Vifor, Bayer, Merck, Sanofi, Abbott, and Boehringer Ingelheim. M.M. has received personal fees from Amgen, Livanova, and Vifor Pharma as a member of executive committees of sponsored clinical trials and from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Lifesciences, and Roche Diagnostics for participation to advisory boards or for speaking at sponsored meetings. C.E. is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. O.C. received grants from Servier. R.D. has received supporting fees for coordination of STRONG-HF trial activities. G.F. has received lecture fees or was a committee member for trials and registries sponsored by Bayer, Vifor, Boehringer Ingelheim, Medtronic, Servier, and Amgen. K.S. has received grants from Medtronic, Servier, and Amylam and honoraria from MSD, Novartis, and Sanofi. A.A.V. has received consultancy fees or research support from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Myocardia, Merck, Novartis, Novo Nordisk, and Roche Diagnostics. MN is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. KT is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. A.D. works for the Faculty of Medicine, Eduardo Mondlane University (Maputo, Mozambique), which received research grants from the Heart Initiative for their participation in this study. P.S.P. has received grants or research contracts from American Heart Association, Roche, Siemens, Ortho Diagnostics, Abbott, Beckman Coulter, and Siemens; consulting fees from Roche; honoraria from WebMD; and he has financial interest in The Heart Course. J.C. has received personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, and Pfizer. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Redcardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder and non-executive director of Us2.ai. M.P. has received personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim and Vifor Pharma. MA has received speaker fees from Abbott Vascular and Medtronic. M.B. is employee of Momentum Research, which has received grants for research from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Corteria Pharmaceuticals, Heart Initiative, Sanofi, Windtree Therapeutics, and XyloCor Therapeutics. The other authors have no conflicts to report.

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