



The influence of comorbidities on achieving an N-terminal pro-b-type natriuretic peptide target: a secondary analysis of the GUIDE-IT trial

Justin A. Ezekowitz^{1*} , Wendimagegn Alemayehu¹ , Sarah Rathwell² , Andrew D. Grant³,
Mona Fiuzat⁴ , David J. Whellan⁵ , Tariq Ahmad⁶, Kirkwood Adams⁷, Ileana L. Piña⁸ ,
Lawton S. Cooper⁹ , James L. Januzzi¹⁰ , Eric S. Leifer⁹ , Daniel Mark⁴ ,
Christopher M. O'Connor¹¹ and G. Michael Felker⁴

¹Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada; ²Women and Children's Health Research Institute, University of Alberta, Edmonton, AB, Canada; ³Department of Cardiac Sciences, Cumming School of Medicine, University of Calgary, and the Libin Institute of Cardiovascular Research, Calgary, AB, Canada; ⁴Division of Cardiology, Duke University School of Medicine, Durham, NC, USA; ⁵Department of Medicine, Thomas Jefferson University, Philadelphia, PA, USA; ⁶Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, CT, USA; ⁷Division of Cardiology, University of North Carolina, Chapel Hill, NC, USA; ⁸School of Medicine, Wayne State University, Detroit, MI, USA; ⁹National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA; ¹⁰Massachusetts General Hospital Harvard Medical School, and Baim Institute for Clinical Research, Boston, MA, USA; and ¹¹Inova Heart and Vascular Institute, Falls Church, VA, USA

Abstract

Aims N-terminal pro-b-type natriuretic peptide (NT-proBNP) values may be influenced by patient factors beyond the severity of illness, including atrial fibrillation (AF), renal dysfunction, or increased body mass index (BMI). We hypothesized that these factors may influence the achievement of NT-proBNP targets and clinical outcomes.

Methods A total of 894 patients with heart failure with reduced ejection fraction were enrolled in The Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment trial. NT-proBNP was analysed every 3 months.

Results Forty per cent of patients had AF, the median estimated glomerular filtration rate (eGFR) was 59 mL/min/1.73 m² [interquartile range (IQR) 43–76], and median BMI was 29 kg/m² (IQR 25–34). Patients with AF, eGFR < 60 mL/min/1.73 m², or a BMI < 29 kg/m² had a higher level of NT-proBNP at randomization and over all study visits (all *P* values < 0.001). Over 18 months, the rate of change of NT-proBNP was less for patients with AF (compared with those without AF, *P* = 0.037) and patients with an eGFR < 60 mL/min/1.73 m² (compared with eGFR > 60 mL/min/1.73 m², *P* < 0.001). The rate of change of NT-proBNP was similar for patients with a BMI above or below the median value. Using the 90 day NT-proBNP, patients with AF, lower eGFR, or lower BMI were less likely to achieve the target NT-proBNP < 1000 pg/mL than patients without AF, higher eGFR, or higher BMI, respectively. None of these differed between the Usual Care or Guided Care arm for AF, eGFR, or BMI (*P*_{interactions} all NS).

Conclusions Patients with AF, a lower BMI, or worse renal function are less likely to achieve a lower or target NT-proBNP. Clinicians should be aware of these factors both when interpreting NT-proBNP levels and making therapeutic decisions about heart failure therapies.

Keywords Heart failure; Atrial fibrillation; Clinical trial; Obesity; Natriuretic peptides

Received: 16 June 2021; Revised: 19 August 2021; Accepted: 28 October 2021

*Correspondence to: Justin A. Ezekowitz, Canadian VIGOUR Centre, University of Alberta, Edmonton, AB, Canada. Tel: 1-780-492-0712, Email: jae2@ualberta.ca
ClinicalTrials.gov Identifier: NCT01685840

Introduction

Patients with heart failure (HF) often have an elevated N-terminal pro-b-type natriuretic peptide (NT-proBNP), which identifies a population at higher risk for clinical events such

as hospitalization or death. In recognition of its value for serial prognostication during HF therapy, measurement of NT-proBNP is often used in the longitudinal follow-up of patients with HF, with therapy decision-making based on NT-proBNP concentrations. However, interpretation of

NT-proBNP must be placed in clinical context. Important considerations in understanding an NT-proBNP concentration include comorbidities that may elevate or lower the value the severity of HF. Circumstances in which this is particularly noteworthy include in patients with chronic renal disease and atrial fibrillation, in whom values of NT-proBNP are higher than explained by HF alone.^{1,2} Additionally, some conditions such as obesity^{3–5} may have discordant effects on natriuretic peptides (NPs). These factors may ultimately lead to differences in clinical management.

To test the clinical benefits of biomarker-guided care for HF, the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) randomized clinical trial was performed in the United States and Canada, comparing NT-proBNP-guided HF management vs. Usual Care.⁶ Patients in the biomarker-guided arm were treated with usual care plus a goal to suppress NT-proBNP to less than 1000 pg/mL, whereas those in the Usual Care arm received standard clinically guided approaches to treatment decisions. NT-proBNP targets were not adapted to clinical features (such as obesity or renal dysfunction), and the trial enrolled a broadly generalizable population of patients with HF with reduced ejection fraction (HFrEF). No difference in achieved NT-proBNP concentrations or treatment intensity between the two study arms was reported; however, those patients achieving an NT-proBNP < 1000 pg/mL by 90 days had considerably better subsequent prognosis than those who did not and had greater reverse cardiac remodelling.⁷

We hypothesized that baseline factors may make it less likely to achieve the NT-proBNP to the target used in the GUIDE-IT trial. We specifically explored the relationship of atrial fibrillation, renal disease, and obesity to both the baseline NT-proBNP and the change in NT-proBNP over time. We additionally explored the association of achieving the target NT-proBNP in the GUIDE-IT trial (<1000 pg/mL), medication changes, and clinical outcomes associated with these three clinically relevant factors.

Methods

Study design and setting

The GUIDE-IT trial design and outcomes have been previously reported.⁶ GUIDE-IT was a multicentre randomized clinical study, conducted from 16 January 2013 to 20 September 2016, that tested the strategy of augmented guideline based therapy to suppress NT-proBNP concentrations to less than 1000 pg/mL vs. Usual Care. The GUIDE-IT trial enrolled 894 patients with HF with an ejection fraction of 40% or less, a history of a HF event within the prior 12 months, and an NT-proBNP level of >2000 pg/mL or BNP of >400 pg/mL in the last 30 days. The enrolled patients were randomized in

a 1:1 fashion to an NT-proBNP guided or Usual Care treatment arm. The study was approved by the institutional review board at each study site, and all participants provided written informed consent.

Participants and comparison groups

All patients enrolled in GUIDE-IT, regardless of randomization arm, were included. Patients were classified into groups identifying comorbidity conditions as: atrial fibrillation (yes/no by past medical history), chronic kidney disease [estimated glomerular filtration rate (eGFR) < 60 vs. ≥60 mL/min/1.73 m²], and obesity [body mass index (BMI) > median value]. Furthermore, for quantification of the degree of renal dysfunction and obesity, the eGFR and BMI, respectively, were analysed as continuous variables. Of the 894 patients enrolled, 0 patients had missing data on atrial fibrillation, 31 patients had missing data on eGFR, and 21 patients had missing data on BMI.

Variables

Baseline and other variables were collected during the conduct of the overall GUIDE-IT trial. BMI was calculated as the ratio between weight and height squared (kg/m²). A history of atrial fibrillation was collected at baseline, and renal function is described using the eGFR at the randomization visit. BMI and eGFR were treated as continuous variables. NT-proBNP was measured at baseline and every 3 months thereafter by protocol. NT-proBNP was available for all patients at baseline, 638 (78.1%) at 90 days and 376 (42.1%) at 12 months. Other values are available in Supporting information, *Table S1*.

Outcomes

The primary clinical outcome was the composite outcome of time to first HF hospitalization (HFH) or cardiovascular death (CVD). We secondarily looked at the individual outcomes of CVD, HFH, and all-cause mortality. The main biomarker outcome for this study was whether a patient achieved a NT-proBNP ≤ 1000 pg/mL by 90 days. We additionally explored medication changes at each time point as per prior studies.⁸

Statistical analysis

Descriptive data were summarized as frequencies and percentages for categorical variables and medians with 25th and 75th percentiles (interquartile range) for continuous variables. The relationships at baseline of atrial fibrillation

status, eGFR, and BMI with NT-proBNP at baseline and with the serial NT-proBNP over time were evaluated. The continuously measured eGFR, BMI, and NT-proBNP were first log-transformed, and pairwise Pearson's correlation coefficients were estimated. The longitudinal NT-proBNP profile over time was compared between the groups in each of the three comorbid conditions. The longitudinal profile over time was first explored graphically and using a flexible generalized additive model based on cubic regression splines. It was observed that the mean profile was non-linear and could be approximated by piecewise linear functions of time. A mixed effects model with a piecewise linear fixed effects structure was assumed and was compared between the groups. The fixed effects component includes the comorbidity comparison groups and their interaction with time, and the adjustment covariate. Random intercept and random slope terms were included to take into account the correlation among serial measurements. The covariates used for adjustment are those in previously established GUIDE-IT predictive model that include ethnicity, duration of HF, New York Heart Association (NYHA) class, ischaemic heart disease, obstructive sleep apnoea, heart rate, diastolic blood pressure, sodium, creatinine, implantable cardioverter-defibrillator, congestion score, and baseline log NT-proBNP.⁹

The association of each of the comorbid conditions with the likelihood of achieving the NT-proBNP under the target level of below 1000 pg/mL by 90 days \pm 2 weeks was assessed using a multivariable logistic regression adjusting for the same covariates in the predictive model. The eGFR and BMI were analysed as continuous variables, and the linearity assumption of the relationship was tested by fitting the restricted cubic spline regression (*Figure S1*). Using the suggested inflection points from the fit, piecewise linear relationships were assumed to estimate the respective odds ratio (OR) and 95% confidence interval (CI) per unit change in the continuous variables. Patients from both arms combined were analysed, but stratified by arm estimates were provided if there was an indication for modifying effect of treatment arm assignment.

The association of the comorbidities with tendency of medication change (yes/no) as an outcome was modelled. Multivariable logistic regression that allows for flexibility of the relationship through a piecewise linear model was applied. Whether there was medication change was assessed over the entire follow-up visits, and the method of generalized estimating equations was applied to take into account the correlation among outcomes in repeated visits of the same patient.

Cox proportional hazard regression model was applied to evaluate the effect of each of the conditions on the clinical outcomes. Hazard ratios (HR) and 95% CI were estimated in adjusted analyses with the same set of adjustment covariates described earlier. Furthermore, the restricted cubic spline regression fit was used to assess the linearity assumption

and appropriate transformation was applied in the Cox model. Kaplan–Meier curves comparing the cumulative event rates between the conditions were generated. A two-sided $P < 0.05$ was regarded as significant. Statistical analyses were performed with SAS, Version 9.4 (SAS Institute, Inc.) and R statistical software, Version 3.6.3 (R Project for Statistical Computing).

Results

In the GUIDE-IT trial, the median age was 63 years, 32% were female, and 40% had atrial fibrillation. The median ejection fraction was 24% (95% CI 20, 30), the median eGFR was 59 mL/min/1.73 m² (95% CI 43, 76), and median BMI was 29 kg/m² (95% CI 25, 34). Patient characteristics varied based on the presence or absence of atrial fibrillation, the eGFR, and by BMI (*Table 1*). Patients with atrial fibrillation were more likely to be older and have higher NT-proBNP and a lower eGFR. Patients with lower eGFR were more likely to be older and female. Patients with lower BMI were more likely to be older. Other baseline characteristics are as per *Table 1*. Baseline NT-proBNP was correlated to BMI (correlation -0.227 , P value < 0.0001 , *Figure 1A*), eGFR (-0.340 , P value < 0.0001 , *Figure 1B*), and atrial fibrillation (higher NT-proBNP in patients with atrial fibrillation, P value < 0.0002 , *Figure 1C*); eGFR and BMI were not correlated (*Figure 1D*).

Temporal N-terminal pro-b-type natriuretic peptide changes

Using values of NT-proBNP from baseline through to the end of study, the relationship between NT-proBNP and atrial fibrillation, and eGFR and BMI was found to be non-linear. Patients with atrial fibrillation, eGFR < 60 mL/min/1.73 m² or a BMI < 28.76 kg/m² had a higher level of NT-proBNP at randomization and over all study visits (all P values < 0.001 , *Figure 2*). Using the first 18 months of data, the rate of change was greater for patients without atrial fibrillation compared with those with atrial fibrillation, ($P = 0.04$) and patients with an eGFR > 60 mL/min/1.73 m² (compared with those with an eGFR < 60 mL/min/1.73 m², $P < 0.001$). The rate of change was similar for patients with a BMI above or below the median value. After 18 months, the rate of change was similar across all comparisons.

Achievement of N-terminal pro-b-type natriuretic peptide target

Using the 90 day NT-proBNP, patients with atrial fibrillation were less likely to achieve the target NT-

Table 1 Baseline characteristics by comparative groups' atrial fibrillation status, eGFR, and BMI at randomization

| | AFIB | | eGFR (mL/min/1.73 m ²) | | BMI | |
|--|------------------|------------------|------------------------------------|------------------------|------------------------|----------------------|
| | No (N = 749) | Yes (N = 145) | > = 60 (N = 419) | <60 (N = 444) | > = 28.76 (N = 437) | <28.76 (N = 436) |
| Age (years), median (IQR) | 61 (51–70) | 68 (60–76) | 57 (48–67) | 66 (58–75) | 59 (50–67) | 66 (56–75) |
| Women, n, % | 250 (33.38%) | 36 (24.83%) | 116 (27.68%) | 156 (35.14%) | 157 (35.93%) | 119 (27.29%) |
| Race/Ethnicity | | | | | | |
| White | 396 (54.32%) | 94 (66.20%) | 214 (51.82%) | 266 (61.72%) | 221 (52.25%) | 261 (60.98%) |
| Black or African American | 288 (39.51%) | 36 (25.35%) | 176 (42.62%) | 134 (31.9%) | 185 (43.74%) | 133 (31.7%) |
| Other | 44 (5.87%) | 11 (7.59%) | 20 (4.77%) | 30 (6.76%) | 15 (3.43%) | 34 (7.80%) |
| Duration of HF (months) | 11 (1–60) | 34 (4–108) | 6 (1–48) | 28 (4–84) | 24 (1–84) | 8 (1–48) |
| Median (IQR) | | | | | | |
| LVEF at baseline, median (IQR) | 23 (20–30) | 25 (20–34) | 20 (15–27) | 25 (20–32.3) | 24 (20–30) | 23 (19.5–30) |
| NYHA class at enrolment | | | | | | |
| I | 56 (7.59%) | 3 (2.10%) | 037 (8.94%) | 19 (4.33%) | 25 (5.77%) | 33 (7.66%) |
| II | 378 (51.22%) | 69 (48.25%) | 229 (55.31%) | 201 (45.79%) | 204 (47.11%) | 236 (54.76%) |
| III | 291 (39.43%) | 67 (46.85%) | 143 (34.54%) | 207 (47.15%) | 194 (44.80%) | 155 (35.96%) |
| IV | 13 (1.76%) | 4 (2.80%) | 5 (1.21%) | 12 (2.73%) | 10 (2.31%) | 7 (1.62%) |
| Missing | 11 (1.47%) | 2 (1.38%) | 5 (1.19%) | 5 (1.13%) | 4 (0.92%) | 5 (1.15%) |
| Medical history | | | | | | |
| Ischaemic heart disease | 377 (50.40%) | 70 (48.28%) | 169 (40.33%) | 262 (59.1%) | 192 (43.94%) | 245 (56.19%) |
| Diabetes | 340 (45.39%) | 70 (48.28%) | 153 (36.52%) | 244 (54.95%) | 236 (54.00%) | 167 (38.30%) |
| Atrial fibrillation | 749 | 145 | 52 (12.56%) | 88 (20.0%) | 72 (16.67%) | 72 (16.71%) |
| BMI, median (IQR) | 28.8 (24.5–34) | 28.9 (24.8–33.5) | 28.3 (24.5–33.6) | 29 (24.8–34.2) | 33.8 (30.9–38.8) | 24.6 (22.4–26.5) |
| Missing | 20 | 1 | 7 | 11 | 0 | 0 |
| Heart rate (beats/min), median (IQR) | 76 (67–87) | 78 (69–83) | 78 (69–88) | 75 (66–84) | 78 (68–88) | 76 (67–85) |
| Systolic BP (mmHg), median (IQR) | 114 (101–130) | 112 (102–123) | 114 (100–129) | 113.5 (102–128) | 116 (103–130) | 112 (100–126) |
| NT-proBNP at baseline, median (IQR) | 2485 (1358–5156) | 3609 (2071–6019) | 2014 (1060–3616) | 3623.5 (1928.5–7000.5) | 2054 (1213–3792) | 3476.5 (1775.5–6983) |
| eGFR (mL/min/1.73 m ²), median (IQR) | 60.5 (44.3–78.6) | 50.9 (38.9–68.2) | 77.2 (67.5–89.2) | 43.3 (34.8–51.8) | 57.8 (41.5–75.3) | 60.3 (43.6–77.5) |
| Missing | 26 | 5 | 0 | 0 | 18 | 10 |
| Sodium (mmol/L), median (IQR) | 139 (136–141) | 138 (136–141) | 139 (136–141) | 138 (136–141) | 139 (136–141) | 138 (136–141) |
| Treatments | | | | | | |
| Beta blocker | 693 (92.90%) | 138 (95.17%) | 396 (94.51%) | 411 (92.57%) | 405 (92.68%) | 409 (93.81%) |
| ACE/ARB | 576 (77.21%) | 108 (74.48%) | 366 (87.35%) | 295 (66.44%) | 334 (76.43%) | 336 (77.60%) |
| Implantable cardioverter-defibrillator | 297 (39.65%) | 063 (43.45%) | 143 (34.13%) | 205 (46.17%) | 186 (42.56%) | 165 (37.84%) |
| Cardiac resynchronization | 124 (16.56%) | 39 (26.90%) | 49 (11.69%) | 108 (24.32%) | 86 (19.68%) | 73 (16.74%) |
| Treatment arm | | | | | | |
| Biomarker-guided | 378 (50.47%) | 68 (46.90%) | 215 (51.31%) | 215 (48.42%) | 216 (49.43%) | 217 (49.77%) |
| Usual care | 371 (49.53%) | 77 (53.10%) | 204 (48.69%) | 229 (51.58%) | 221 (50.57%) | 219 (50.23%) |

ACE, angiotensin converting enzyme; AFIB, atrial fibrillation; ARB, angiotensin converting enzyme; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-b-type natriuretic peptide; NYHA, New York Heart Association.

proBNP < 1000 pg/mL than patients without atrial fibrillation [adjusted OR (adjOR) 0.46 (95% CI 0.23, 0.93), $P = 0.03$] (Table 2). For patients with an eGFR ≤ 90 mL/min/1.73 m², patients were less likely to achieve the target NT-proBNP < 1000 pg/mL with each decreasing 1 mL/min/1.73 m² [adjOR 0.97 (95% CI 0.95, 0.98), $P < 0.001$]. Once eGFR was >90 mL/min/1.73 m², there was no significant relationship between changes in eGFR and odds of achieving the target NT-proBNP < 1000 pg/mL [adjOR 0.98 (95% CI 0.95, 1.00), $P = 0.057$]. Similarly for BMI, for patients with BMI ≤ 40 , patients were less likely to achieve the target NT-proBNP < 1000 pg/mL with each decreasing BMI unit [adjOR 0.88 (95% CI 0.83, 0.93), $P < 0.001$]. Once BMI was >40 kg/

m², there was no significant relationship between changes in BMI and odds of achieving the target NT-proBNP < 1000 pg/mL [adjOR 0.94 (95% CI 0.88, 1.01), $P < 0.089$]. However, none of these differed between the Usual Care or Guided Care arm for atrial fibrillation, eGFR, or BMI ($P_{\text{interaction}}$ all NS).

Changes in medications

The relationship of the three comorbid conditions to medication changes is presented in Table 3. There was no association between a history of atrial fibrillation with medication changes [adjOR 0.95 (95% CI 0.76, 1.2), $P = 0.69$], and this

Figure 1 Correlation of baseline NT-proBNP to BMI (A), eGFR (B), atrial fibrillation (C), and correlation between BMI and eGFR (D). BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-b-type natriuretic peptide.

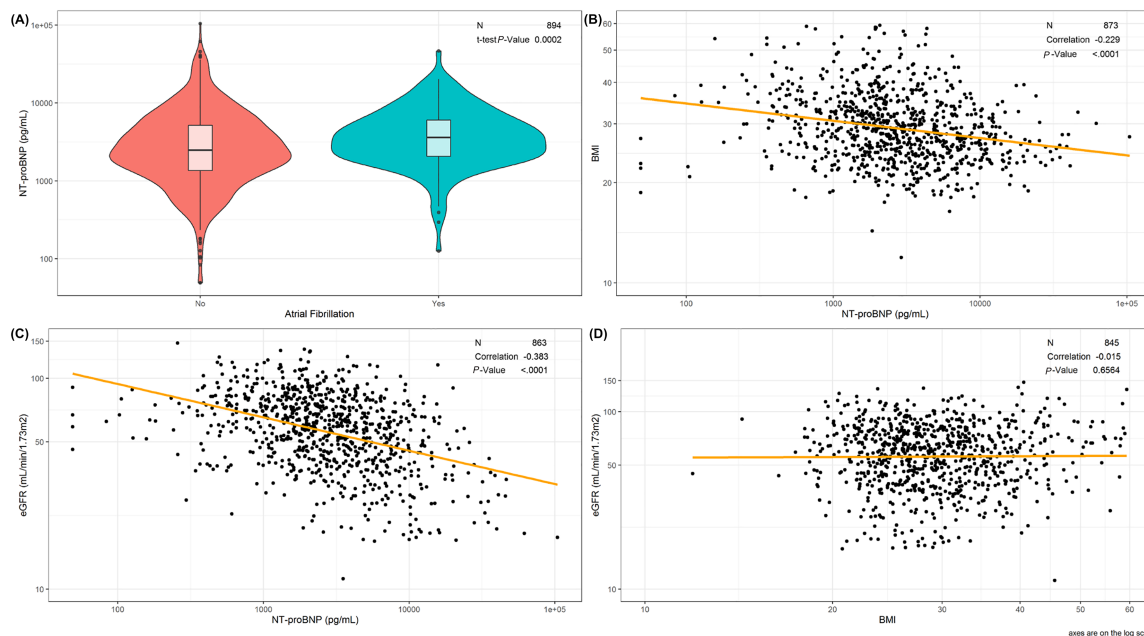
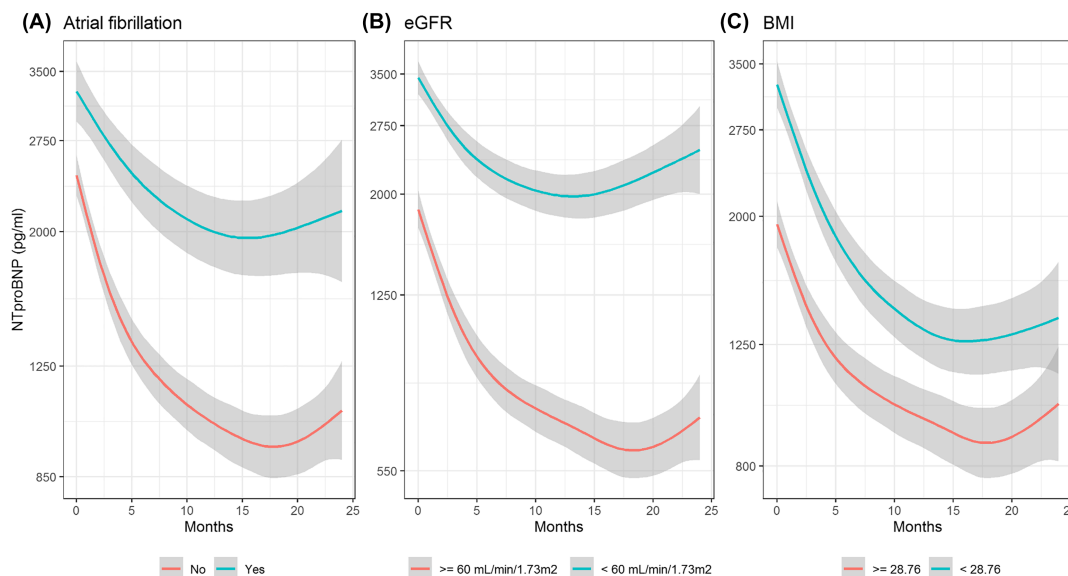


Figure 2 The longitudinal profile of NT-proBNP over the visit months by baseline AF status (A), eGFR (B), and BMI (C). AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-b-type natriuretic peptide.



did not differ between the Usual Care or Guided Care arm ($P_{\text{interaction}} = 0.24$). Similarly, for patients using BMI as a continuous analysis or above or below a BMI of 29, there was no association with medication changes, and this did not differ between the Usual Care or Guided Care arm ($P_{\text{interaction}} = 0.75$). For renal function, the relationship was complex. For

example, there was a relationship between eGFR (above or below 60 mL/min/1.73 m²) and medication changes, with patients with a higher eGFR more likely to have medication changes; however, this relationship was non-significant [adjOR 1.18 (95% CI 0.98, 1.41), $P = 0.073$]. Additionally, an interaction of eGFR with randomized treatment group was

Table 2 Associations of baseline atrial fibrillation, renal function, and BMI with the likelihood of achieving NT-proBNP target by 90 days

| Comorbid condition | Adjusted ^a OR (95% CI) | P | P-interaction between treatment group and comorbid condition |
|---|-----------------------------------|--------|--|
| Atrial fibrillation (yes vs. no) | 0.46 (0.23–0.93) | 0.030 | 0.91 |
| eGFR (per unit increase mL/min/1.73 m ²) if ≤90 | 1.03 (1.02–1.05) | <0.001 | 0.38 |
| eGFR (per unit increase mL/min/1.73 m ²) if >90 | 0.98 (0.95–1.00) | 0.057 | 0.77 |
| eGFR (<60 vs. ≥60 mL/min/1.73 m ²) | 0.38 (0.24–0.61) | <0.001 | 0.27 |
| BMI (per unit increase kg/m ²) if ≤40 | 1.12 (1.07–1.17) | <0.001 | 0.51 |
| BMI (per unit increase kg/m ²) if >40 | 0.94 (0.88–1.01) | 0.089 | 0.24 |
| BMI (<29 vs. ≥29 kg/m ²) | 0.46 (0.28–0.74) | 0.001 | 0.23 |

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, heart disease; HF, heart failure; NT-proBNP, N-terminal pro-b-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio.

^aAdjusted for ethnicity, duration of HF, NYHA class, ischaemic HD, obstructive sleep apnoea, heart rate, diastolic blood pressure, sodium, creatinine, implantable cardioverter-defibrillator, congestion score, and NT-proBNP; however, do not include creatinine for the analysis of eGFR. An odds ratio (OR) < 1 indicates less, while >1 indicates better chance of achieving target NT-proBNP level.

Table 3 Associations of baseline comorbid conditions with the likelihood of a medication change

| Comorbid condition | Adjusted ^a OR (95% CI) | P | P-interaction between treatment group and comorbid condition |
|--|-----------------------------------|-------|--|
| Atrial fibrillation (yes vs. no) | 0.95 (0.76–1.2) | 0.688 | 0.24 |
| eGFR (per unit increase mL/min/1.73 m ²) if ≤90 | 1 (0.99–1) | 0.142 | 0.056 |
| eGFR (per unit increase mL/min/1.73 m ²) if > 90 | 1 (0.99–1.01) | 0.502 | 0.61 |
| eGFR (<60 vs. ≥60 mL/min/1.73 m ²) | 1.18 (0.98–1.41) | 0.073 | 0.008 |
| Usual care | 1 (0.77–1.29) | 0.978 | |
| Guided therapy | 1.32 (1.04–1.66) | 0.022 | |
| BMI (per unit increase kg/m ²) if ≤40 | 0.99 (0.98–1.01) | 0.43 | 0.35 |
| BMI (per unit increase kg/m ²) if >40 | 1.04 (1.01–1.07) | 0.022 | 0.91 |
| BMI (<29 vs. ≥29 kg/m ²) | 1 (0.84–1.2) | 0.985 | 0.75 |

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, heart disease; HF, heart failure; NT-proBNP, N-terminal pro-b-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio.

^aAdjusted for ethnicity, duration of HF, NYHA class, ischaemic HD, obstructive sleep apnoea, heart rate, diastolic blood pressure, sodium, creatinine, implantable cardioverter-defibrillator, congestion score, and NT-proBNP; however, do not include creatinine for the analysis of eGFR

noted ($P_{\text{interaction}} = 0.008$). In the Usual Care arm, there was no association between continuous eGFR and medication changes [adjOR 1.0 (95%CI 0.77, 1.29), $P = 0.978$], but for the Guided Care arm, there was [adjOR 1.32 (95%CI 1.04, 1.66), $P = 0.022$], indicating that these patients were more likely to have a medication change if the eGFR > 60 mL/min/1.73 m². However, there were no differences from baseline to 12 months in the guideline medication intensity score for patients with or without atrial fibrillation, by eGFR or by BMI (Table S2).

Clinical outcomes

Figure 3 summarizes the effects of each of the conditions on the clinical outcomes. The risk for CVD/HFH was lower in patients with atrial fibrillation compared with patients without atrial fibrillation [adjusted HR 0.60 (95% CI 0.41, 0.87), $P = 0.008$], and there was an indication of an interaction between the Usual Care and Guided Care arms ($P_{\text{interaction}} = 0.055$). Renal function, by either continuous eGFR or dichotomized at eGFR 60 mL/min/1.73 m², was associated with the outcome of CVD/HFH, but there was no inter-

action between the Usual Care and Guided Care arms. BMI, by continuous values, was associated with the outcome of CVD/HFH [adjusted HR 1.02 per kg/m² (95%CI 1.0 to 1.04), $P = 0.06$], but there was no interaction between the Usual Care and Guided Care arms. Other outcomes of all-cause mortality, all-cause hospitalization, and HFH are shown in Figure 3. Kaplan–Meier survival curves comparing the cumulative event rates by individual comorbid condition are shown in Figure 4 (for the primary outcome), and Figure S2 presents similar curves for the secondary outcomes.

Comorbidity interactions

To further explore the additive interaction of the comorbid conditions with each other, achievement of the 90 day NT-proBNP and clinical outcomes, interaction terms were explored. First, three-way interaction effect of the comorbid conditions exists on the association with likelihood of achieving target NT-proBNP by 90 days ($P_{\text{interaction}} = 0.036$) but was not a significant interaction with medication change ($P_{\text{interaction}} = 0.16$). There was a non-significant additive effect of the number of comorbid conditions. For every additional

Figure 3 Effects of comorbid conditions on primary and secondary clinical outcomes. AFIB, atrial fibrillation; aHR, adjusted hazard ratio; BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure.

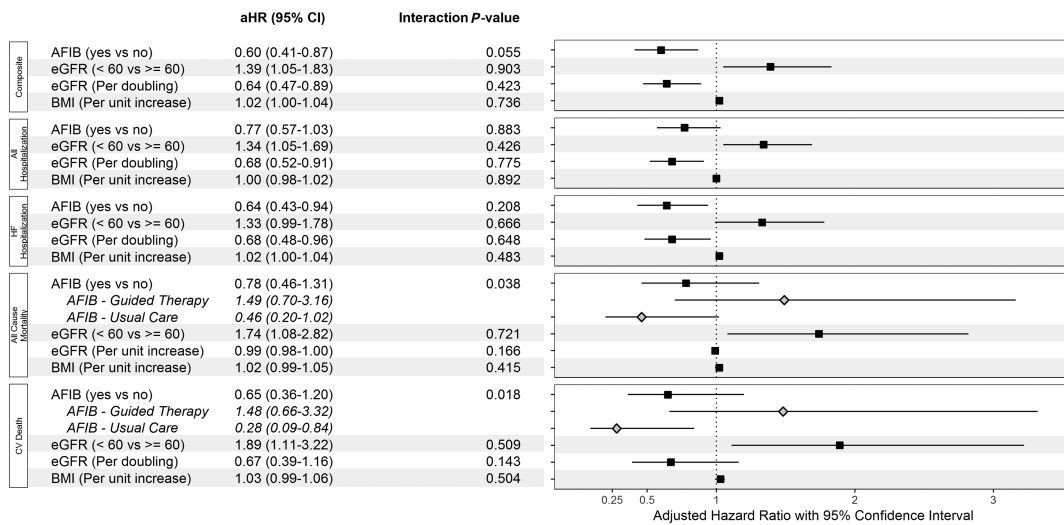
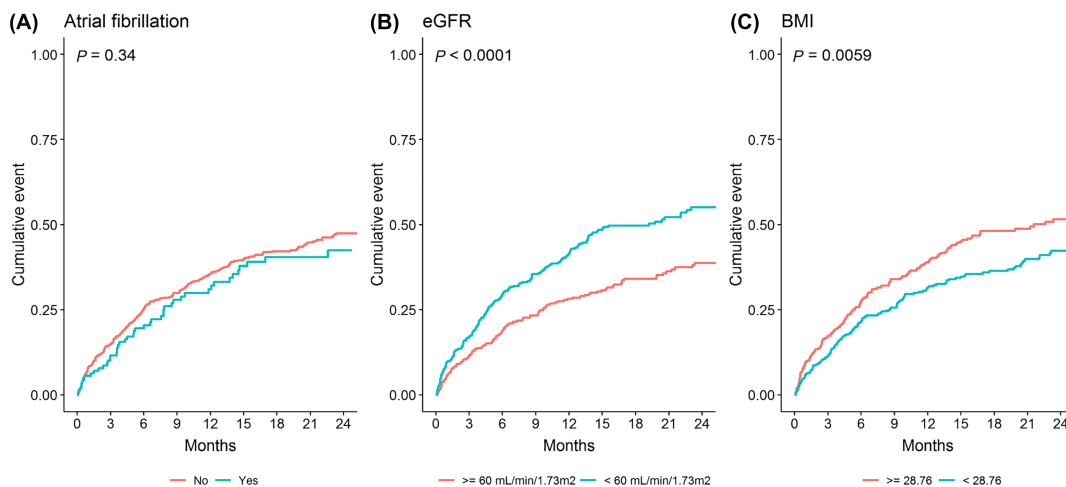


Figure 4 Kaplan–Meier curve of time to primary clinical outcome, according to AF status (A), renal function (B), and obesity category (C). AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate.



comorbid condition, after adjustment for other variables, the likelihood of achieving the 90 day target NT-proBNP decreases by 18% [OR: 0.82 (95% CI 0.62, 1.1), $P = 0.18$]; however, this was non-statistically significant. Additional comorbidities were not associated with changes in medication or dose intensity.

Discussion

Comorbidities may affect the management of patients with HFREF. In this secondary analysis of the GUIDE-IT trial, we

explored the impact of important comorbidities common in clinical practice and their impact on the biomarker NT-proBNP and achievement of NT-proBNP targets. We identified three key findings that will influence clinical practice. First, patients with atrial fibrillation, renal dysfunction, and a lower BMI had a higher NT-proBNP at baseline and throughout the 18 month follow-up. Clinicians should be aware that the values they see in practice should be viewed in this context and that not all patients should be viewed through the same lens for management based on NT-proBNP. Secondly, the rate of change of NT-proBNP over time was slower for patients with atrial fibrillation and renal dysfunction, but

similar across a range of BMI. This indicates the ability to change the key biomarker NT-proBNP may be slower than anticipated in patients with HFrEF, given that atrial fibrillation and impaired renal function are common comorbidities (atrial fibrillation is present in ~40% of patients and ~50% have an eGFR < 60 mL). Third, the ability to achieve the protocol-specified GUIDE-IT target of NT-proBNP < 1000 pg/mL differed if patients had one or more of these three key comorbid conditions. For example, patients with atrial fibrillation were 56% less likely to achieve the fixed target by 90 days. Similar results were seen for patients with renal dysfunction or with a lower BMI, and the majority of patients did not come close to the target set for GUIDE-IT. These findings indicate the need to consider personalization of targets to be inclusive of multiple factors.

Patients with renal dysfunction have additional risk for poor outcomes, and hence, targeting a lower NT-proBNP would seem in theory to potentially reduce their risk. However, targeting a NT-proBNP similar to those patients without renal dysfunction may not be as easily achievable and selecting a value such as that in GUIDE-IT (<1000 pg/mL) rather than a personalized value may not lead to success in a reduction in clinical events. On the other hand, in addition to the difficulty to achieve the set target NT-proBNP level for patients with AF, the additional risk for poor outcome (especially CV death and mortality) seems to be greater among patients in the GUIDE-IT treatment arm; this remains to be further understood. Many patients with HF have greater than one comorbidity,^{10,11} and this burden may be reflected in outcomes or the achievement of a biomarker goal. For example, the additive effect of an additional one of the three comorbidities reduced the ability to achieve the short-term biomarker goal of NT-proBNP < 1000 pg/mL at 90 days by 18%. This reduced ability to achieve the target may subsequently lead to difficulty in achieving the clinical outcome reduction. A prior publication utilizing the same dataset and looking at the serial changes of NT-proBNP as it relates to BMI (examined as single dichotomized factor) demonstrated that patients with obesity have a lower NT-proBNP level and similar use of medical therapy.¹² Our finding is concordant with the prior meta-analysis (that does not include GUIDE-IT) that comorbid conditions (rather than age alone) influence outcomes as well as the potential for a guided approach efficacy.¹³ We extend those results by using continuous variables, interactions and with a sizable population with a high event rate allowing us to discern these findings with greater and fidelity. There remains uncertainty as to why patients with AF in the Usual Care arm (compared with the GUIDE-IT treatment arm) had lower risk for all-cause or CV mortality, which was consistent after adjustment but may be related to trial design, inclusion criteria, or other confounding not available in the collected data. The majority of patients with AF did not have a meaningful reduction in NT-proBNP com-

pared with those without AF, and perhaps, alternate markers should be sought for these patients with a combination of HF and AF.

Limitations

This study has several important strengths and limitations. First, given the nature of the study intervention, the study was unblinded, which could be a potential source of bias as investigative teams at the site would have been aware of the baseline NT-proBNP values as well as the BMI, renal function, and presence of atrial fibrillation. However, as there was no difference in statistical interaction between the guided and control arms, this is less likely to be relevant, and in addition, NT-proBNP was collected by protocol on all patients every 3 months. Second, although there was a highly generalizable population enrolled into the overall trial, there were few people with a very low eGFR (e.g. eGFR < 30 mL/min/1.73 m²) or extremes of BMI. Nevertheless, the patients enrolled represent the majority of higher risk patients with HFrEF in North America. Third, as with all secondary or post-hoc analyses, unmeasured confounders may in part explain part of the association between NT-proBNP, outcomes, and individual comorbidities.

Conclusions

In this secondary analysis of the GUIDE-IT trial, we identified that the three common comorbid conditions of renal dysfunction, atrial fibrillation, and obesity have important effects on natriuretic peptide concentrations. Importantly, all three of these conditions were related to a different level of baseline NPs, and this relationship persisted throughout the duration of the trial. The presence of atrial fibrillation and renal dysfunction made it very difficult to achieve the target set for GUIDE-IT, was associated with a slower rate of change of NPs, and was associated with fewer medication changes. Clinical trials studying the outcomes related to NPs, or targeting NPs, should consider carefully setting a personalized target rather than a fixed target for all patients. Clinicians should heed the results when interpreting individual NP changes seen in practice.

Acknowledgements

We would like to acknowledge the contributions of the GUIDE-IT investigators, study coordinators, and the participating patients to the GUIDE-IT study. Additionally, we would like to acknowledge Dr Cynthia Westerhout for analytical guidance and Lisa Soulard for editorial support.

Conflict of interest

None declared.

Funding

The GUIDE-IT trial was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Additional substudies were supported by Roche Diagnostics. The sponsors had no role in the design and conduct of the present study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

- Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi JL Jr. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: Results from the ProBNP investigation of dyspnea in the emergency department (PRIDE) study. *J Am Coll Cardiol* 2006; **47**: 91–97.
- Morello A, Lloyd-Jones DM, Chae CU, van Kimmenade RRJ, Chen AC, Baggish AL, O'Donoghue M, Lee-Lewandrowski E, Januzzi JL Jr. Association of atrial fibrillation and amino-terminal pro-brain natriuretic peptide concentrations in dyspneic subjects with and without acute heart failure: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *Am Heart J* 2007; **153**: 90–97.
- Krauser DG, Lloyd-Jones DM, Chae CU, Cameron R, Anwaruddin S, Baggish AL, Chen A, Tung R, Januzzi JL Jr. Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: A ProBNP investigation of dyspnea in the emergency department (PRIDE) substudy. *Am Heart J* 2005; **149**: 744–750.
- Das Sandeep R, Drazner Mark H, Dries Daniel L, Vega Gloria L, Stanek Harold G, Abdullah Shuaib M, Canham Russell M, Chung Anne K, David L, Wians Frank H, de Lemos James A. Impact of body mass and body composition on circulating levels of natriuretic peptides. *Circulation* 2005; **112**: 2163–2168.
- Selvaraj S, Kim J, Ansari BA, Zhao L, Cvijic ME, Fronheiser M, Mohan-Rao Vanjarapu J, Kumar AA, Suri A, Yenigalla S, Satija V, Ans AH, Narvaez-Guerra O, Herrera-Enriquez K, Obeid MJ, Lee JJ, Jehangir Q, Seiffert DA, Car BD, Gordon DA, Chirinos JA. Body composition, natriuretic peptides, and adverse outcomes in heart failure with preserved and reduced ejection fraction. *JACC Cardiovasc Imaging* 2021; **14**: 203–215.
- Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL Jr, Mark DB, Piña IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA* 2017; **318**: 713–720.
- Daubert MA, Adams K, Yow E, Barnhart HX, Douglas PS, Rimmer S, Norris C, Cooper L, Leifer E, Desvigne-Nickens P, Anstrom K, Fiuzat M, Ezekowitz J, Mark DB, O'Connor CM, Januzzi J, Felker GM. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFREF. *JACC Heart Fail* 2019; **7**: 158–168.
- Fiuzat M, Ezekowitz J, Alemayehu W, Westerhout CM, Sbolli M, Cani D, Whellan DJ, Ahmad T, Adams K, Piña IL, Patel CB, Anstrom KJ, Cooper LS, Mark D, Leifer ES, Felker GM, Januzzi JL, O'Connor CM. Assessment of limitations to optimization of guideline-directed medical therapy in heart failure from the GUIDE-IT trial: a secondary analysis of a randomized clinical trial. *JAMA* 2020; **5**: 757–764.
- O'Connor C, Fiuzat M, Mulder H, Coles A, Ahmad T, Ezekowitz JA, Adams KF, Piña IL, Anstrom KJ, Cooper LS, Mark DB, Whellan DJ, Januzzi JL Jr, Leifer ES, Felker GM. Clinical factors related to morbidity and mortality in high-risk heart failure patients: The GUIDE-IT predictive model and risk score. *Eur J Heart Fail* 2019; **21**: 770–778.
- Bhatt AS, Ambrosy AP, Dunning A, DeVore AD, Butler J, Reed S, Voors A, Starling R, Armstrong PW, Ezekowitz JA, Metra M, Hernandez AF, O'Connor CM, Mentz RJ. The burden of non-cardiac comorbidities and association with clinical outcomes in an acute heart failure trial – insights from ASCEND-HF. *Eur J Heart Fail* 2020; **22**: 1022–1031.
- Sharma A, Zhao X, Hammill BG, Hernandez AF, Fonarow GC, Felker GM, Yancy CW, Heidenreich PA, Ezekowitz JA, DeVore AD. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: Insights from the get with the guidelines-heart failure registry: Insights from the get with the guidelines-heart failure registry. *Circ Heart Fail* 2018; **11**: e004646.
- Parcha V, Patel N, Kalra R, Suri SS, Arora G, Wang TJ, Arora P. Obesity and

Supporting information

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

Figure S1. Continuous relationship of eGFR and BMI with the likelihood of achieving NT-proBNP under the target (below 1000 pg/mL) by 90 days+/- 2 weeks. eGFR, estimated glomerular filtration rate; BMI, body mass index; NT-proBNP, N-terminal pro-b-type natriuretic peptide.

Figure S2. K-M curves time to secondary outcome events according to comorbid conditions. eGFR, estimated glomerular filtration rate; BMI, body mass index; HF, heart failure; CV, cardiovascular.

Table S1. Patients with NT-proBNP results at baseline and during follow-up.

Table S2. Type and intensity of medication at baseline and during follow-up.

- serial NT-proBNP levels in guided medical therapy for heart failure with reduced ejection fraction: Insights from the GUIDE-IT trial. *J Am Heart Assoc* 2021; **10**: e018689.
13. Brunner-La Rocca H-P, Eurlings L, Richards AM, Januzzi JL, Pfisterer ME, Dahlström U, Pinto YM, Karlström P, Erntell H, Berger R, Persson H, O'Connor CM, Moertl D, Gaggin HK, Frampton CM, Nicholls MG, Troughton RW. Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials: Which heart failure patients profit from natriuretic peptide guided therapy. *Eur J Heart Fail* 2015; **17**: 1252–1261.