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RESEARCH ARTICLE

N-terminal pro-B-type natriuretic peptide post-discharge monitoring in the management of patients with heart failure and preserved ejection fraction – a randomized trial: The NICE study

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Aims There is a lack of specific studies assessing the impact of natriuretic peptide monitoring in the post-discharge management of patients with heart failure (HF) and preserved ejection fraction (HFpEF), throughout the vulnerable phase following acute HF hospitalization. The NICE study aims to assess the clinical benefit of incorporating N-terminal pro-B-type natriuretic peptide (NT-proBNP) into the post-discharge management of HFpEF patients.

Methods and results Individuals admitted with HFpEF (left ventricular ejection fraction >50%) were included in a multicentre randomized controlled study employing an open-label design with event blinding (NCT02807168). Upon discharge, 157 patients were randomly allocated to either NT-proBNP monitoring ($n = 79$) or no access to NT-proBNP (control group, $n = 78$) during pre-scheduled visits at 2, 4 and 12 weeks. Clinical endpoints were evaluated at 6 months. The primary endpoint of HF rehospitalizations occurred in 12.1% patients, without significant differences observed between the NT-proBNP monitoring group (12.8%) and the control group (11.4%) (hazard ratio [HR] 1.15, 95% confidence interval [CI] 0.47–2.81, $p = 0.760$). Regarding secondary endpoints, the NT-proBNP monitoring group demonstrated a significantly lower risk of death (1.3% vs. 10.1%; HR 0.12, 95% CI 0.02–0.98; $p = 0.048$), whereas non-HF hospitalizations (12.8% vs. 19.0%, $p = 0.171$) and any adverse clinical event (26.9% vs. 36.7%, $p = 0.17$) did not reach statistical significance [Correction added on 29 April 2024, after first online publication: In the preceding sentence, "95% CI 0.02 - 0.09" has been corrected to "95% CI 0.02 - 0.98; p = 0.048" in this version.]. Awareness of NT-proBNP levels were associated with higher doses of diuretics and renin–angiotensin system inhibitors (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers) in the NT-proBNP monitoring group.

Conclusions Post-discharge monitoring of NT-proBNP in HFpEF patients did not exhibit an association with reduced rates of HF hospitalization in this study. Nonetheless, it appears to enhance global clinical management by optimizing medical therapies and contributing to improved overall survival.

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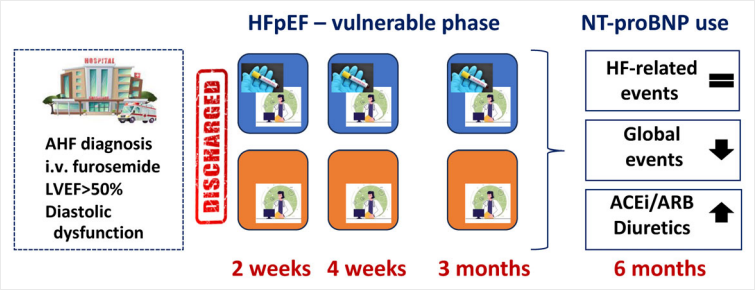
Graphical Abstract



Effects of incorporating N-terminal pro-B-type natriuretic peptide (NT-proBNP) into clinical visits during the post-discharge period of patients with heart failure (HF) and preserved ejection fraction (HFpEF). ACEi, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin II receptor blocker; i.v. intravenous; LVEF, left ventricular ejection fraction.

Keywords Acute heart failure • NT-proBNP • Preserved left ventricular ejection fraction • Randomized trial

Introduction

In patients with heart failure (HF), the post-hospitalization period represents a vulnerable phase characterized by a heightened risk of adverse events. Literature indicates that after discharge, 20% of patients are readmitted within 30 days, and 30–50% experience readmission within the next 6 months.[1] Within the HF landscape, the demographic of patients with HF and preserved ejection fraction (HFpEF) is on the rise, attributed to both aging and comorbidities.[2] Unlike patients with HF and reduced ejection fraction (HFrEF), who have a plethora of available drugs and devices capable of halting disease progression, those with HFpEF have been relatively orphaned. Recently, the introduction of sodium–glucose cotransporter 2 inhibitors (SGLT2i) has shown efficacy, particularly in reducing HF hospitalizations.[3,4] Incorporating management and monitoring strategies, such as decongestion and early follow-up visits, could influence the prognosis of the intricate HFpEF phenotype during the vulnerable post-discharge phase.

Circulating concentrations of natriuretic peptides (NPs) show a strong correlation with severity and prognosis in both chronic and acute HF settings.[5] While numerous trials, mostly with target NP cut-point levels and involving HFrEF populations, have yielded neutral results,[6–10] the recent STRONG-HF trial demonstrated that an intensive optimization strategy of guideline-directed medical therapies (GDMT), initiated before discharge and supported by frequent post-discharge visits, including NP monitoring, is associated with higher rates of GDMT and improved clinical outcomes.[11,12] These results led to the recommendation of this intensive strategy in the recent update of the European Society of Cardiology (ESC) HF guidelines.[4] However, patients with HFpEF have been marginally included in some ambulatory trials[13,14] and represented solely 15% in the STRONG-HF trial.[11] Indeed, no studies have specifically addressed the impact of NP monitoring in HFpEF management after discharge. Nevertheless, given the complexity of the HFpEF phenotype, there is a potential benefit in combining NP measurements with clinical assessment, particularly crucial during the vulnerable post-hospitalization stage. Accordingly, we designed an open-label randomized trial to examine the effects of integrating N-terminal pro-B-type natriuretic peptide (NT-proBNP) monitoring into the post-discharge management of hospitalized HFpEF patients.

Methods

Study design and patient population

This is a multicentre randomized controlled study with an open-label design, blinded to events (PROBE) (ClinicalTrials.gov Identifier: NCT02807168). The study population consisted of hospitalized patients with HFpEF. The inclusion criteria were: (1) the presence at admission of all of the following: dyspnoea at rest or with minimal effort (New York Heart Association [NYHA] class III or IV), pulmonary congestion on chest X-ray, elevated NT-proBNP levels (<50 years: >450 pg/ml; 50–75 years: >900 pg/ml; >75 years: >1800 pg/ml)[15]; and administration of at least 40 mg intravenous furosemide; (2) the presence of left ventricular ejection fraction (LVEF) >50% in the echocardiography performed during the hospitalization, with additional evidence of diastolic dysfunction defined as any of the following parameters: é <8 cm/s septal or <10 cm/s lateral; E/e' ratio >15; A mitral–A pulmonary >30 ms; left atrial volume index ≥34 ml/m^2; left ventricular mass index >95 g/m^2 (female) o >115 g/m^2 (male). The exclusion criteria were: significant lung disease demonstrated by spirometry; life expectancy lower than 6 months; severe valvular disease or other cardiac condition with a planned or expected intervention in the following 6 months; inability to have adhesion at the different visits of the study. Local ethics committees of participating centres approved the study protocol. Patients who accomplished all inclusion and exclusion

criteria were invited to participate, and written informed consent was obtained.

Study protocol

At the time of discharge, subjects were randomized into two groups: usual care (control group) or usual care plus NT-proBNP monitoring (NT-proBNP group). Randomization was controlled by age, sex, atrial fibrillation, hypertension, NYHA functional class, days of hospitalization, left atrial size, number of previous hospitalizations and NT-proBNP at discharge. In both groups, patients were treated according to the contemporary clinical guidelines.[16,17] Randomization was web-based and electronically assisted, by using the minimization method. All patients had the same follow-up clinical visits, which were pre-specified at the following time points: 2, 4 and 12 weeks. Only for those patients allocated to the NT-proBNP monitoring group, the investigators had access to NT-proBNP concentrations at clinical visits and they used NT-proBNP values to adjust medication according to clinical criteria, without specific indications per protocol.

A description of the study design and procedures is provided in *Figure 1*. At each scheduled visit, clinical variables including changes in medication and adverse clinical events were registered. A serum biobank was created at randomization and at each visit. The quality of life was evaluated by Kansas City Cardiomyopathy Questionnaire (KCCQ) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) at randomization, 3 and 6 months. Functional capacity was assessed by a 6-min walking test (6MWT) at randomization and final visit.

Endpoints

The primary study endpoint was the occurrence of rehospitalization due to HF at 6 months, defined as unplanned hospital admission for at least 24 h due to HF decompensation. The secondary endpoints were: (1) worsening HF episodes, defined as impairment of signs and/or symptoms of HF that require the administration of intravenous therapy, with or without hospitalizations; (2) change in quality of life at 3 and 6 months, as assessed by KCCQ and MLHFQ; (3) change in functional capacity at 6 months, evaluated as the distance walked in the 6MWT; (4) mortality, considering all-cause and cardiovascular mortality; (5) all-cause hospitalization; (6) any adverse event defined as any worsening HF episode, any cause hospitalization or death. Alongside assessing efficacy endpoints, we examined changes in medication dosage across the visits as an explanatory endpoint.

Statistical methods

Baseline characteristics were described using mean ± standard deviation and median (interquartile range[IQR]) for continuous variables (according to normality) and frequency (percentage) for categorical variables. Normality was assessed with graphical (Q–Q plots, histograms and boxplots) and analytical methods (Kolmogorov–Smirnov tests). Student's *t*-tests, Wilcoxon rank-sum tests and chi-squared tests were used to determine differences between control and NT-proBNP groups, as appropriate. Clinical events were studied with survival analyses: Kaplan–Meier plots with log-rank test and Cox proportional hazards models were used. To analyse longitudinal changes in drug doses, multilevel regression models were estimated by adjusting for randomization group, time and patient. Least-squares means were calculated to assess differences over time and between groups. The expected rate of HF rehospitalization was 30% at 6 months,[1] and the planned sample size was 210 patients per group to detect a 40% reduction in the primary endpoint, providing a power level of 80% (error $\alpha = 0.05$) and considering a drop-out of 10%. All analyses were conducted using statistical software R (version 4.1) with survival, lmer and Emmeans packages.

Results

Study population

The consort flow diagram of the study is presented in *Figure 1*. A total of 157 patients were randomized into the NT-proBNP monitoring group ($n = 79$) versus the control group ($n = 78$) from 2016 to 2019. A total of 8 patients, four in each group, discontinued prematurely the study (median 92 days, IQR 75–185 days) due to consent withdrawal. The patient's status was obtained without loss of follow-up in any case. The study was prematurely stopped before reaching the planned sample size ($n = 420$) due to COVID-related restrictions and based on anticipated futility for the primary endpoint at the first intermediate analysis (one-third of sample size).

Table 1 presents the clinical characteristics of both groups, which reflects well those typical features of patients with HFpEF. The majority of patients were female (61.0%), with a mean age of 76 years for both sexes. The most prevalent aetiology was hypertensive (36.3%), followed by ischaemic (24.2%) and valvular (21.7%). Atrial fibrillation affected 74.4% of patients. Common comorbidities included diabetes (47.1%) and renal insufficiency (35.1%). Echocardiographic findings revealed increased ventricular mass (mean of 205.8 g), a dilated left atrium (median volume 69 ml), and elevated left ventricular filling pressures (mean E/é of 14). In terms of biochemical parameters, NT-proBNP at baseline (discharge) had a median of 2590 pg/ml. As shown in *Table 1*, no significant differences were observed between the intervention (NT-proBNP) arm and the control arm, including length of hospital stay (median of 7.3 vs. 7.7 days, $p = 0.647$).

Clinical outcomes

The primary endpoint of HF rehospitalizations occurred in 19 (12.1%) patients (*Table 2*). There were no significant differences between the NT-proBNP monitoring group (12.8%) and the control group (11.4%) (hazard ratio [HR] 1.15, 95% confidence interval [CI] 0.47–2.81, $p = 0.760$). Likewise, *Table 2* outlines the distribution of primary and secondary clinical events between NT-proBNP and control arms. No significant differences were found in other worsening HF events, including urgent (14.1% vs. 10.1%) and outpatient visits (9.0% vs. 8.9%). However, the NT-proBNP monitoring group exhibited a significantly lower risk of death (1.3% vs. 10.1%; HR 0.12, 95% CI 0.02–0.98), whereas the lower rate of non-HF-related hospitalizations (12.8% vs. 19.0%, $p = 0.265$) and any adverse event rates (26.9% vs. 36.7%, $p = 0.171$) did not reach statistical significance.

Figure 2 displays the Kaplan–Meier survival analysis for the main adverse outcomes. Patients undergoing NT-proBNP monitoring

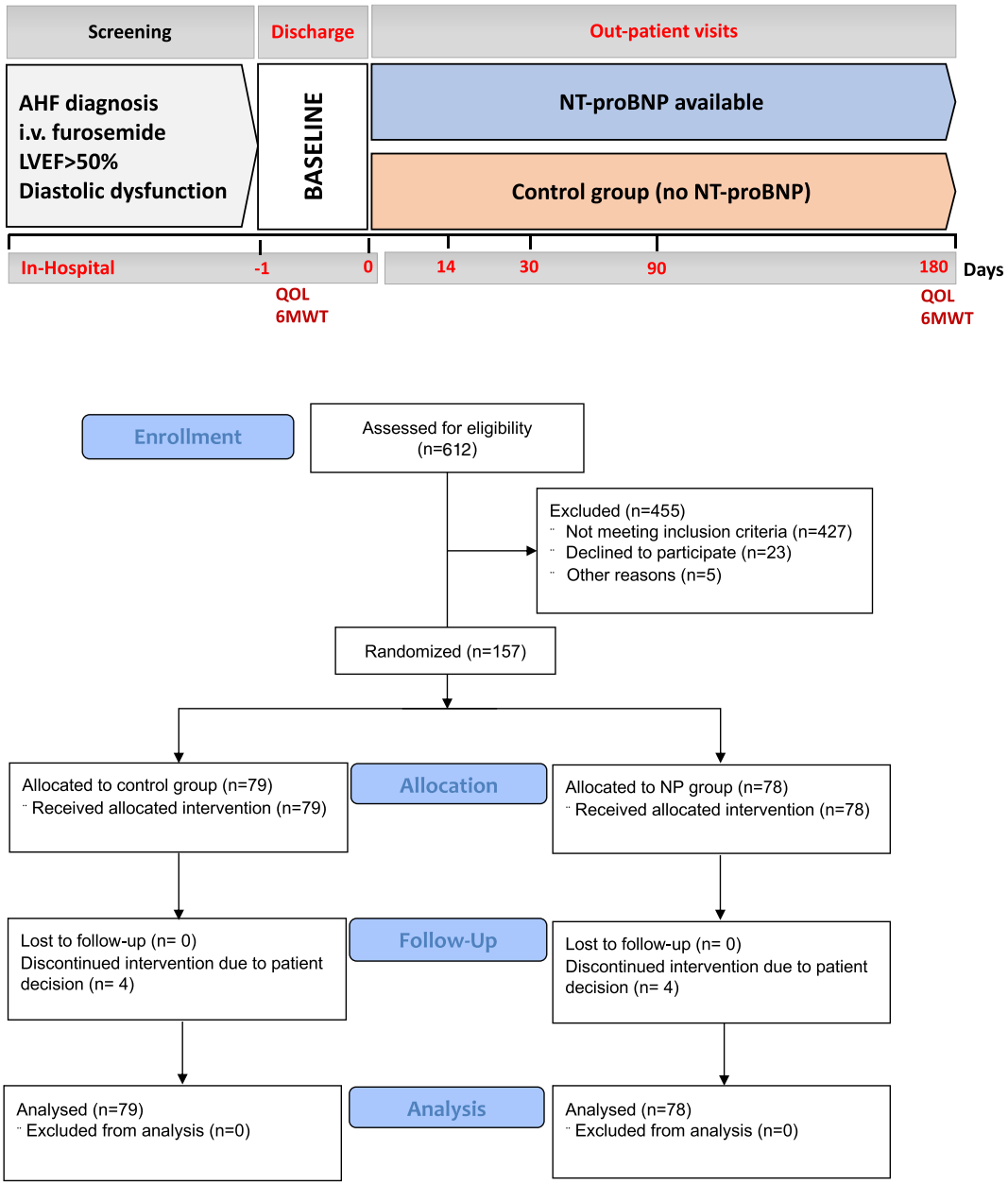


Figure 1 NICE study design and consort flow diagram. 6MWT, 6-min walking test; AHF, acute heart failure; i.v. intravenous; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QOL, quality of life.

exhibited significantly higher survival at 6 months compared to the control group (log-rank 0.018) (*Figure 2B*). Concerning causes of death, most control group patients died due to HF-related causes, with five patients succumbing to refractory HF, two to sudden cardiac death, and one to septic shock; the sole deceased patient in the NT-proBNP group died due to refractory HF.

Post-discharge, both groups showed improved quality of life at 6 months compared to baseline, indicated by MLHFQ (control: -29.6 ± 3.88, $p < 0.001$; NT-proBNP: -35.7 ± 4.21, $p < 0.001$) and KCCQ (control: $+27.7 \pm 3.53$, $p < 0.001$; NT-proBNP: $+21.9 \pm 3.44$, $p < 0.001$), with no significant differences between groups (*Table 2*). Functional capacity, measured by distance walked in the 6MWT, also improved (control: $+48.6 \pm 14.6$, $p = 0.002$; NT-proBNP: $+34.7 \pm 16.5$, $p = 0.040$), with no significant differences between groups (*Table 2*).

Influence on medication dosage

As an exploratory endpoint, we investigated the impact on prescribed doses of diuretics, angiotensin-converting enzyme inhibitors (ACEI) (or angiotensin II receptor blockers [ARB]),

Table 1 Clinical characteristics at inclusion

	Overall	Control arm	NT-proBNP arm	*p*-value
Patients, *n*	157	79	78	
Female sex	95 (60.5)	48 (40.8)	47 (60.3)	1.000
Age, years	76.49 ± 8.59	76.79 ± 8.10	76.18 ± 9.11	0.660
Body mass index, kg/m^2	29.33 ± 6.04	30.03 ± 5.64	28.57 ± 6.40	0.159
History				
Diabetes	74 (47.1)	39 (49.4)	35 (44.9)	0.686
Hypertension	131 (84.0)	65 (82.3)	66 (85.7)	0.714
Hypercholesterolaemia	92 (60.1)	47 (60.3)	45 (60.0)	1.000
Smoking	8 (5.3)	4 (5.3)	4 (5.2)	1.000
Aetiology				0.807
Ischaemic	38 (24.2)	19 (24.1)	19 (24.4)	
Hypertensive	57 (36.3)	27 (34.2)	30 (38.5)	
Valvular	34 (21.7)	20 (25.3)	14 (17.9)	
Other	28 (17.9)	13 (16.5)	15 (19.2)	
Prior HF hospitalization	66 (42.3)	35 (44.9)	31 (39.7)	0.627
Atrial fibrillation	116 (74.4)	58 (73.4)	58 (75.3)	0.929
Myocardial infarction	30 (19.2)	16 (20.3)	14 (18.2)	0.901
Coronary revascularization	37 (24.2)	19 (24.7)	18 (23.7)	1.000
Chronic kidney disease	53 (35.1)	32 (41.0)	21 (28.8)	0.160
Chronic pulmonary disease	12 (7.7)	5 (6.3)	7 (9.2)	0.711
Cerebrovascular disease	12 (8.1)	6 (7.9)	6 (8.3)	1.000
Peripheral vascular disease	13 (8.7)	7 (9.2)	6 (8.2)	1.000
Systolic blood pressure, mmHg	126.63 ± 20.84	125.58 ± 20.88	127.72 ± 20.88	0.527
Diastolic blood pressure, mmHg	67.54 ± 13.39	67.26 ± 12.55	67.83 ± 14.27	0.795
Heart rate, bpm	70 [60–82]	69 [60–83]	70 [60.8–80.5]	0.960
NYHA class				0.262
I–II	124 (81.1)	60 (76.9)	58 (77.3)	
III–IV	29 (19.0)	18 (23.1)	11 (14.7)	
Rhythm				0.605
Sinus rhythm	61 (40.7)	28 (36.8)	33 (44.6)	
Atrial fibrillation/flutter	79 (52.7)	43 (56.6)	36 (48.6)	
Pacemaker	10 (6.7)	5 (6.6)	5 (6.8)	
Laboratory parameters				
Creatinine, mg/dl	1.15 [0.90–1.60]	1.20 [0.90–1.50	1.10 [0.80–1.67]	0.627
Urea, mg/dl	19.99 [13.92–32.13]	19.70 [14.19–28.56]	20.17 [13.84–33.91]	0.640
Sodium, mEq/L	139 [137–141]	139 [137–141]	139 [137–141]	0.908
Potassium, mEq/L	4.25 ± 0.56	4.25 ± 0.60	4.24 ± 0.52	0.941
NT-proBNP, pg/ml	2590 [1269–6065]	2823 [1326–7892]	2246 [1257–4946]	0.176
Haemoglobin, g/L	124.39 ± 19.67	124.13 ± 18.02	124.65 ± 21.34	0.873
Echocardiographic parameters				
LVEF, %	60.59 ± 7.34	61.07 ± 7.46	60.07 ± 7.22	0.425
LV end-diastolic diameter, mm	45.58 ± 7.47	45.15 ± 8.05	46.03 ± 6.84	0.520
LV end-diastolic volume, ml	85.47 ± 32.37	83.59 ± 30.43	87.57 ± 34.72	0.601
Interventricular septum, mm	12 [10–14]	13 [10.8–14]	12 [10–14]	0.318
LV posterior wall, mm	11 [10–13]	11 [10–13]	11 [10–12]	0.771
LV mass (linear method), g	205.79 ± 63.74	204.00 ± 62.59	207.57 ± 65.48	0.783
LA volume, ml	69 [52–95]	71.5 [55.3–93.3]	66 [50.8–107]	0.775
E/e ratio	14 [11–17]	13.5 [11–16]	14 [11–17]	0.528
TAPSE, mm	17.99 ± 4.27	17.95 ± 4.41	18.04 ± 4.14	0.912
Treatments				
Furosemide	143 (91.1)	71 (89.9)	72 (92.3)	0.799
Furosemide dose, mg/day	60 [40–80]	60 [40–80]	40 [40–80]	0.661
MRA	35 (22.3)	17 (21.5)	18 (23.1)	0.966
RAASi (ACEI or ARB)	85 (54.1)	43 (54.5)	42 (53.9)	0.957
Beta-blockers	100 (63.7)	50 (63.3)	50 (64.1)	1.000
Antiplatelets	43 (27.4)	25 (31.6)	18 (23.1)	0.305
Anticoagulation	103 (65.6)	54 (68.4)	49 (62.8)	0.574

Data are presented as *n* (%), mean ± standard deviation, or median (interquartile range).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA; mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAASi, renin–angiotensin–aldosterone system inhibitor; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Study endpoints in the control versus N-terminal pro-B-type natriuretic peptide group

Outcome	NT-proBNP	Control	HR/difference (95% CI)	*p*-value
Clinical outcomes				
Death	1 (1.3)	8 (10.1)	0.12 (0.02–0.98)	0.048
Any worsening HF-related event[a]	16 (20.5)	19 (24.1)	0.89 (0.44–1.82)	0.752
Readmission for HF	10 (12.8)	9 (11.4)	1.15 (0.47–2.81)	0.760
Urgent HF visit	11 (14.1)	8 (10.1)	1.44 (0.58–3.55)	0.429
Unplanned outpatient HF visits[b]	7 (9.0)	7 (8.9)	1.02 (0.36–2.88)	0.974
Death or any HF-related event	16 (20.5)	24 (30.4)	0.65 (0.34–1.22)	0.181
Non-HF-related readmission[a]	10 (12.8)	15 (19.0)	0.64 (0.29–1.41)	0.265
Any adverse event	21 (26.9)	29 (36.7)	0.68 (0.39–1.18)	0.171
HF quality of life measures				
Change in MLHFQ score[c]	−35.7 ± 4.21	−29.6 ± 3.88	−6.17 (−17.5 to 5.20)	0.284
Change in KCCQ QoL score[c]	21.9 ± 3.44	27.7 ± 3.53	−5.84 (−15.6 to 3.92)	0.239
Change in 6-min walking test[c]	34.7 ± 16.5	48.6 ± 14.6	−13.9 (−58.0 to 30.2)	0.532

Data are presented as *n* (%), or mean ± standard error.
CI, confidence interval; HF, heart failure; HR, hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life.
[a]Considering death as a competing event.
[b]Leading to use of intravenous diuretics.
[c]Changes from baseline to final visit.

beta-blockers, and mineralocorticoid receptor antagonists (MRA) at each visit. Patients assigned to the NT-proBNP monitoring group received higher doses of diuretics and ACEI/ARB compared to the control group, while beta-blockers and MRA doses remained similar (*Figure 3*).

Discussion

This randomized study offers new insights into a clinically relevant scenario, specifically on the vulnerable phase after discharge, addressing the management of the challenging HFpEF phenotype. We observed that the availability of NT-proBNP monitoring at post-discharge clinical visits was associated with a neutral effect in the primary endpoint of HF rehospitalizations at 6 months. However, noteworthy findings emerged in some secondary and exploratory analyses: mortality was significantly lower in the NP monitoring group, and patients allocated to NT-proBNP monitoring received higher doses of diuretics and ACEI/ARB (*Graphical Abstract*).

This is the first study specifically designed to evaluate the impact of NP monitoring in the post-discharge follow-up of HFpEF patients. A large number of randomized trials have assessed the impact of NP-guided therapy in HFrEF populations, but they have shown controversial results.[6–10] Indeed, current guideline recommendation for monitoring NP is low (IIb class) and not clearly supported by meta-analysis.[18–20] Nevertheless, HFpEF has been excluded or under-represented (≈10%) in most of these trials.[14] Maeder *et al.*[21] (TIME-CHF trial) were the only to study separately 123 ambulatory patients with chronic HFpEF (defined as LVEF >45%), and randomized to NT-proBNP-guided therapy group ($n = 59$) or symptom-guided group ($n = 64$). In addition, no effect was observed in symptom relief and adverse clinical events, despite more frequent adjustments of treatments in the NT-proBNP-guided group.[21] These results were in the same direction in an individual patient meta-analysis from Brunner-La Rocca *et al.*,[22] that extracted HFpEF patients from four studies (including TIME-CHF) for a total of 144 patients assigned to the NP-guided group and 152 to the control group. In all these studies, NP-guided therapy was assessed in outpatient visits and chronic HFpEF, and no data exist in the setting of acutely decompensated HFpEF.

The present study adds new evidence about the potential benefit of incorporating NT-proBNP monitoring into the post-discharge follow-up of HFpEF patients. We did not find significant differences in the risk of the primary endpoint of HF rehospitalization; nevertheless, we observed a significantly lower risk of death and a non-significant trend to lower the risk of any adverse event in the NT-proBNP group. To interpret these results, we can posit several potential explanations. First, the rate of HF rehospitalization in both study groups was notably lower than previously reported, affecting only 12% of patients at 6 months, as opposed to the 30–50% rate found in various reports a decade ago.[1] Indeed, HF readmissions were only a minority when considering any adverse event rate (32%). It is well established that HFpEF is a complex disease, where comorbidities and non-HF-related events are more prevalent than in HFrEF patients.[23,24] Consequently, to discern between 'true' worsening HF episodes versus non-HF events becomes challenging for the clinician. In this scenario, NPs could play a crucial role in accurately diagnosing worsening HF episodes, thereby facilitating prompt treatment and hospitalization and preventing the progression towards more serious adverse events. Moreover, NPs could also contribute to correctly ruling out worsening HF events, enabling effective management of non-HF complications and comorbidities. Both aspects complement each other, collectively contributing to improved rates of accurately

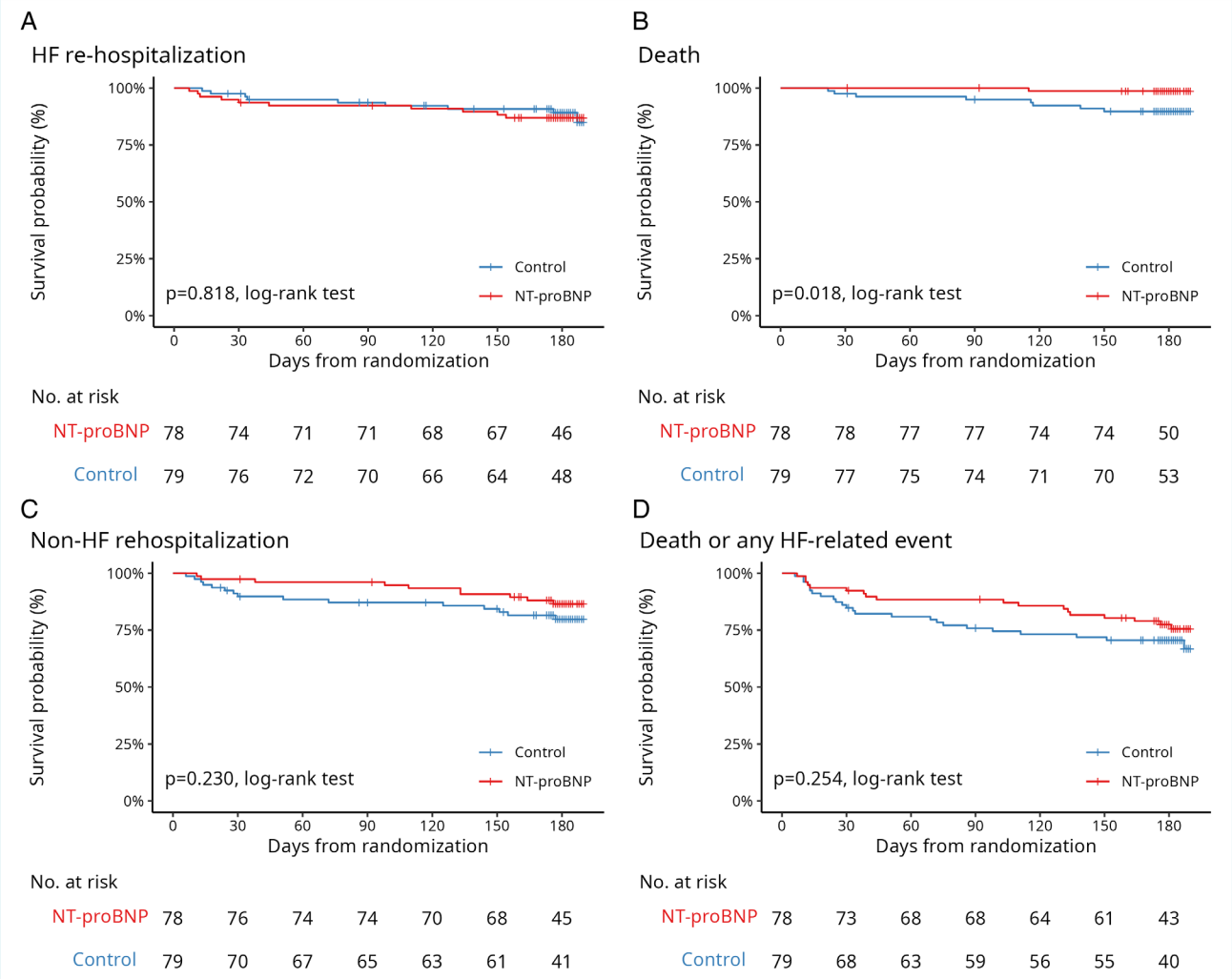


Figure 2 Kaplan–Meier survival curves by study group and for each clinical endpoint. HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

diagnosed HF and non-HF episodes. The overarching goal is to prevent more serious complications and to enhance the overall management of patients with HFpEF. Hence, it is reasonable to appraise the significance of NPs in HFpEF by considering their impact on overall adverse clinical events, including those that may not be directly associated with HF. Indeed, in the present study, an 'apparent' neutral effect was observed in the rate of diagnosed worsening HF events, but we found significantly lower mortality (mostly due to HF-related causes, 89%), and a tendency towards a decreased rate of any adverse clinical event (26.9% in the NT-proBNP monitoring group vs. 36.7% in the control group).

These findings indicate a widespread influence on disease management, consistent with the advantages highlighted in the STRONG-HF trial. They imply that it is not solely about guiding therapy based on NT-proBNP levels, but rather about integrating NT-proBNP information to enhance comprehensive clinical decision-making in a complex condition like HFpEF.

The present study used a pragmatic approach, which is closer to real life than most of the trials that have used an NP-level targeting approach. This approach aligns more closely with the STRONG-HF trial design, where NT-proBNP was accessible in the intensive arm, aiding in the optimization of diuretics and the gradual up-titration of GDMT during the initial 2 weeks.[12,25] In a post-hoc analysis of the STRONG-HF trial, the benefit of intensive follow-up was independent of LVEF.[26] In addition to complementing the STRONG-HF trial, which predominantly enrolled HFrEF patients (only 15% with LVEF ≥50%), the NICE study also shows an improvement in diuretics and ACEI/ARB doses in the arm with NT-proBNP availability, which reflects that information provided by NT-proBNP was also incorporated into therapeutic decisions. It is worth noting that in the Maeder *et al.* study[21] the strategy guided by NT-proBNP showed higher rates of beta-blocker usage (43% vs. 11%, $p < 0.001$), but no significant differences in diuretic doses (25% vs. 13%, $p = 0.018$), which may reflect the impact of the targeting versus no targeting approach, as well as the chronic versus post-acute setting. In addition, part of the benefit in the STRONG-HF trial may be attributed to the close follow-up incorporated in the high-intensity group: during the first 90 days,

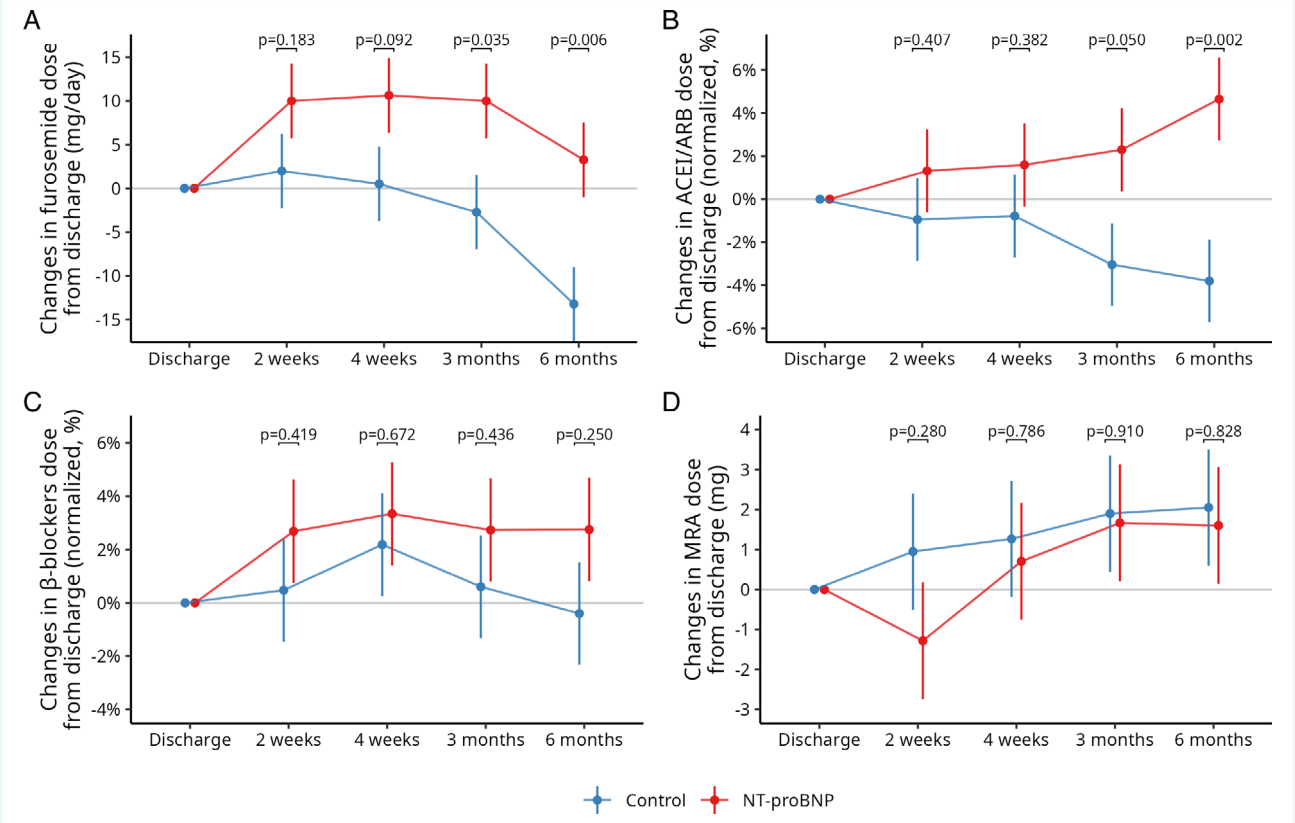


Figure 3 Changes in pharmacological therapies by study group. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

they had a mean of 4.8 visits versus 1.0 visits in the usual care group.[11] In the NICE study, clinical follow-up visits were the same for both arms (three within the first 90 days), which may have limited a more substantial impact on clinical events.

We acknowledge certain limitations, such as the lack of sample size power to reach definitive conclusions and the unblinded design inherent to the NT-proBNP use. The relatively small sample size and number of events limits findings and, therefore, the observed difference in mortality may be due to chance. Nevertheless, this study provides new information about the benefit of incorporating NT-proBNP monitoring to clinical visits during the vulnerable phase after discharge in HFpEF patients, which aligns, in a certain sense, with the results observed in the STRONG-HF trial. Both HFpEF and the post-discharge period are quite relevant for HF practitioners and have a direct translation to disease management programmes. Finally, very recently, SGLT2i have demonstrated improvements in the prognosis of HFpEF and, only a few months ago, they received the highest recommendation in the ESC update on HF guidelines.[3,4] While conducting the NICE trial, SGLT2i were not part of the specified interventions, yet their inclusion might have influenced the outcomes. During that period, there was no comprehensive GDMT for HFpEF, and the standard of care strategies involved adjusting the dose of diuretics and ACEI/ARB.

In conclusion, the findings from the NICE randomized trial suggest that integrating NT-proBNP monitoring into clinical visits during the post-discharge phase of HFpEF patients may yield a beneficial impact. While it may not directly reduce rates of HF hospitalizations, it appears to enhance global clinical management by optimizing medical therapies and contributing to improved overall survival. However, the underpowered sample size makes necessary further studies in larger populations.

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Appendix A

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