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Journal of the American Heart Association

ORIGINAL RESEARCH

Heart Failure With Preserved Ejection Fraction and Lower Natriuretic Peptide: Clinical Characteristics and Change in Natriuretic Peptide Levels

Kanako Teramoto, MD, PhD, MPH; Kotaro Nochioka, MD, PhD, MPH; Yasuhiko Sakata, MD, PhD; Kunihiro Nishimura, MD, PhD, MPH; Hiroaki Shimokawa, MD, PhD; Satoshi Yasuda, MD, PhD; on behalf of the SUPPORT Trial Investigators*

BACKGROUND: Recent heart failure (HF) guidelines emphasize the importance of recognizing patients with mild elevations in NT-proBNP (N-terminal pro-B-type natriuretic peptide). While NT-proBNP is a key biomarker for diagnosing HF and predicting outcomes, its levels are often lower than expected in HF with preserved ejection fraction.

METHODS: Using data from the SUPPORT (Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients With Stable Heart Failure Using Olmesartan) trial, we examined the temporal changes in NT-proBNP and long-term outcomes in patients with HF with preserved ejection fraction (left ventricular ejection fraction ≥50%) categorized by NT-proBNP levels (≤55, 55–125, 125–300, and ≥300 pg/mL).

RESULTS: Among 602 patients with HF with preserved ejection fraction, 335 (55.6%) had NT-proBNP <300 pg/mL (12.5% with ≤55, 18.1% with 55–125, and 25% with 125–300 pg/mL). Patients with NT-proBNP <300 pg/mL were younger and had higher body mass index, more ischemic heart disease, less cardiac remodeling, and lower risks of HF hospitalization or all-cause death compared with those with NT-proBNP ≥300 pg/mL. Over 3 years, 52 (15.5%) patients with NT-proBNP <300 pg/mL, including 40 with 125 to 300 pg/mL, experienced NT-proBNP increase to ≥300 pg/mL, accompanied by left ventricular end-systolic enlargement and left ventricular ejection fraction decline. Importantly, these patients had comparable risks of HF hospitalization or all-cause death as compared with those with persistently elevated NT-proBNP ≥300 pg/mL (adjusted hazard ratio, 1.08 [95% CI, 0.69–1.69]).

CONCLUSIONS: More than half of patients with HF with preserved ejection fraction had NT-proBNP <300 pg/mL at baseline. Patients with mild elevations in NT-proBNP may progress to overt elevations over time, accompanied by cardiac deterioration and adverse outcomes.

Key Words: heart failure with preserved ejection fraction ■ natriuretic peptide ■ N-terminal pro-B-type natriuretic peptide

Recent heart failure (HF) guidelines provide a referral benchmark of NT-proBNP (N-terminal pro-B-type natriuretic peptide) 125 pg/mL for suspected HF.[1–23] However, patients with HF with preserved ejection fraction (HFpEF) often exhibit NT-proBNP levels below this threshold. Natriuretic peptide (NP) levels are notably lower in HFpEF compared with HF with reduced ejection fraction, not

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CLINICAL PERSPECTIVES

What Is New?

- More than half of patients with heart failure with preserved ejection fraction had NT-proBNP (N-terminal pro-B-type natriuretic peptide) <300 pg/mL at baseline, with fewer comorbidities and better outcomes than those with NT-proBNP ≥300 pg/mL in general.
- However, patients with heart failure with preserved ejection fraction and NT-proBNP <300 pg/mL at baseline, particularly those with mild elevation (125–300 pg/mL), experienced an increase in NT-proBNP to ≥300 pg/mL over time, accompanied by structural and functional cardiac deteriorations.

What Are the Clinical Implications?

- The risk of the composite of heart failure hospitalization and all-cause death after 3 years was comparable between patients who experienced an overt elevation of NT-proBNP at 3 years and those who had persistently elevated NT-proBNP in the preceding years, indicating awareness of long-term progression in patients with a mild elevation in natriuretic peptides.

Nonstandard Abbreviations and Acronyms

GDF15	growth differentiating factor-15
HFpEF	heart failure with preserved ejection fraction
KaRen	Karolinska–Rennes
NP	natriuretic peptide
SUPPORT	Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients With Stable Heart Failure Using Olmesartan

only at diagnosis but throughout the disease course.[4] Nevertheless, the prognostic value of NP in HFpEF has consistently demonstrated its undeniable benefit in risk stratification.[5–7]

The Japanese Heart Failure Society recently issued a statement on NP levels in HF management to raise awareness of subtle or marginal elevations in NP levels.[8] In the statement, individuals with BNP ≤18.4 pg/mL or NT-proBNP ≤55 pg/mL were classified as having an extremely low likelihood of HF, while those with BNP 18.4 to 35 pg/mL or NT-proBNP 55 to 125 pg/mL were considered at risk but less likely to require immediate treatment. Individuals with mild NP elevations, BNP 35 to 100 pg/mL or NT-proBNP 125 to 300 pg/mL, were identified as potentially having HF with cardiac abnormalities despite no typical symptoms. While HFpEF with "normal" or "lower" NP levels (eg, NT-proBNP <125 pg/mL) have gained attention, mild NP elevations (eg, NT-proBNP 125–300 pg/mL) are also frequently encountered in clinical practice. However, the prevalence, clinical characteristics, temporal NP changes, cardiac abnormalities, and outcomes of patients with HFpEF with preclinically elevated NT-proBNP remain unclear. Given the differences in characteristics of patients with HFpEF worldwide,[9] it is important to understand NT-proBNP trends in the Asian population to improve patient characterization and develop targeted treatment strategies.

The SUPPORT (Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients With Stable Heart Failure Using Olmesartan; NCT00417222) trial is a prospective, randomized study of Japanese patients with hypertension and HF,[10,11] providing long-term follow-up data ideal for addressing knowledge gaps in Japanese patients with HFpEF. While the trial was performed to assess the impact of olmesartan, an angiotensin receptor blocker, on morbidity and death, the trial collected detailed clinical and biomarker data, including NT-proBNP. In the present study, we thus aimed to explore clinical characteristics, temporal changes in NT-proBNP, and outcomes of Japanese patients with HFpEF across a wide range of NT-proBNP levels. We hypothesized that a long-term increase in NT-proBNP is prognostically important in patients with mildly elevated NT-proBNP at baseline.

METHODS

Patient Population

The sharing of the data supporting this study's findings may be considered by the corresponding author at a reasonable request. The SUPPORT trial is a prospective, randomized, and open-label blinded end point study in which Japanese patients with hypertension and HF were enrolled from October 2006 to March 2010. The study aimed to determine the efficacy of olmesartan, in addition to the use of angiotensin-converting enzyme inhibitors and/or β blockers, for reducing morbidity and death.[13,14] A total of 1147 patients aged between 20 and 80 years across 17 institutes in the Tohoku district were randomized into 2 groups: the olmesartan group (5–10 mg/day olmesartan, uptitrated to 40 mg/day when possible) and a control group with standard treatment. The diagnosis of HF was made by cardiologists on the basis of the Framingham criteria at the time of study enrollment, independent of the NP levels.[12] Anamnestic interview, standard physical assessments, a 12-lead ECG, blood sample collection, and conventional transthoracic

echocardiography were performed at baseline and the 3-year visit. Cardiovascular end points were studied for at least 3 years from the baseline, and end points were adjudicated by blinded reviewers. The trial adheres to the ethical principles of the Declaration of Helsinki and has obtained institutional review board approval across all participating institutions. All participants provided written informed consent.

In the present study, we defined HFpEF as those with left ventricular ejection fraction (LVEF) ≥50%. Thus, we analyzed the data from 602 HFpEF patients (52.5% of the total participants of the SUPPORT trial).

Measurement of NT-proBNP and NP–HFpEF Groups

Serum NT-proBNP concentrations and other biomarkers, such as GDF15 (growth differentiating factor-15), hs-TnT (high-sensitivity troponin T), and CRP (C-reactive protein), were measured using blood samples obtained at baseline and 3-year visits. NT-proBNP was measured with an electrochemiluminescence sandwich immunoassay using a Cobas analyzer (Roche Diagnostics, Indianapolis, IN).

In the present study, patients with HFpEF were categorized into 4 NT-proBNP groups: NT-proBNP ≤55 pg/mL, 55 to 125 pg/mL, ≤125 to 300 pg/mL, and ≥300 pg/mL on the basis of the statement by the Japanese Heart Failure Society.[8] The same cut-off values were used to assess NT-proBNP levels at 3 years to describe the changes in NT-proBNP levels from baseline to 3 years. To further determine the impact of the temporal change in NT-proBNP levels from baseline to 3 years on clinical outcomes after 3 years, patients were categorized into 4 groups of temporal changes in NT-proBNP levels: patients who persistently had NT-proBNP <300 pg/mL at baseline and 3 years, patients who experienced a decrease in NT-proBNP to <300 pg/mL (ie, "improved"), patients who experienced an increase in NT-proBNP to ≥300 pg/mL (ie, "worsened"), and patients who persistently had NT-proBNP ≥300 pg/mL at baseline and 3 years. The group definitions and number of patients subjected to each analysis are demonstrated in Figure S1. As shown in Figure S1, patients with unavailable NT-proBNP measurements at 3 years were omitted from the analysis involving 3-year measurements.

Study End Point

The cardiovascular outcome events collected in the SUPPORT trial were all adjudicated by the Endpoint Evaluation Committee.[13,14] The end point of the present study was the composite of HF hospitalization and all-cause death.

Statistical Analysis

Clinical characteristics at baseline are expressed as means±SDs or medians with interquartile ranges (IQRs). ANOVA was used to determine the difference across the NT-proBNP groups for the normally distributed continuous variables, determined by the Shapiro–Wilk test. Similarly, the χ^2/Fisher's exact test was used for the frequencies of categorical variables. Given their skewed distribution, the Kruskal–Wallis rank-sum test was used for the biomarkers in the laboratory data. Comparisons of NT-proBNP concentrations between baseline and 3 years were performed using a paired Wilcoxon test, in which the biomarker levels were log-transformed before the statistical comparisons. The cumulative incidence of the primary end points is graphically presented with the number of events and event rate in 100 person-years. The risk of the study end points was assessed using the Cox proportional hazard regression models. Given the potential influence of confounding factors on the level of NT-proBNP and outcomes, age, sex, body mass index, New York Heart Association class, history of diabetes, and estimated glomerular filtration rate at baseline were adjusted in the multivariable models. The Schoenfeld residuals were tested for proportional hazard assumptions. The risks of the study end points after 3 years were estimated using the multivariable Cox proportional hazard regression models for those with NT-proBNP measurement available at baseline and 3 years. All statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed *P* value of <0.05 was considered to be statistically significant.

RESULTS

HFpEF With Lower NT-proBNP

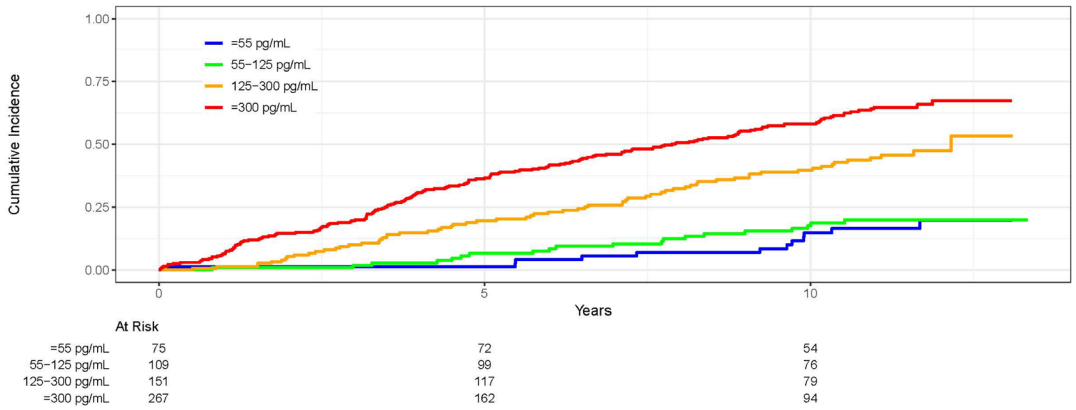
The studied patients consisted of 602 patients with HFpEF, with a mean age of 66 years and 30% women. Around half of the patients had each of the comorbidities of diabetes, dyslipidemia, or ischemic heart disease. Only 6% had New York Heart Association class III, and their median NT-proBNP concentration was 255 (IQR, 103–655) pg/mL. Among 602 patients with HFpEF, 335 (55.6%) had NT-proBNP <300 pg/mL, including 75 (12.5%) with NT-proBNP ≤55 pg/mL, 109 (18.1%) with NT-proBNP 55 to 125 pg/mL, and 151 (25.0%) with NT-proBNP 125 to 300 pg/mL. Compared with those with NT-proBNP ≥300 pg/mL who were older with borderline renal function, patients with NT-proBNP <300 pg/mL were younger and had a higher body mass index, a higher prevalence of dyslipidemia and ischemic heart disease, and a lower prevalence of atrial fibrillation, with less

Table Clinical Characteristics Across NT-proBNP Groups at Baseline 4

	Overall	NT-proBNP groups				ANOVA *P* value
		≤55 pg/mL	55–124 pg/mL	125–300 pg/mL	≥300 pg/mL	
N, n (%)	602	75 (12.5)	109 (18.1)	151 (25.0)	267 (44.4)	NA
Demographics						
Age, y	66.4 (9.9)	58.8 (12.4)	64.9 (10.0)	66.3 (9.8)	69.3 (7.5)	<0.001
Female sex, n (%)	179 (29.7)	18 (24.0)	26 (23.9)	46 (30.5)	89 (33.3)	0.197
Weight, kg	63.1 (12.7)	70.2 (15.9)	64.7 (10.8)	62.3 (11.4)	60.9 (12.5)	<0.001
Body mass index, kg/m^2	24.5 (4.1)	26.2 (5.0)	24.7 (3.8)	24.4 (4.0)	24.0 (3.9)	0.001
NYHA class III, n (%)	36 (6.0)	7 (9.3)	4 (3.7)	6 (4.0)	19 (7.1)	0.238
Medical history, n (%)						
Diabetes	289 (48.0)	34 (45.3)	54 (49.5)	75 (49.7)	126 (47.2)	0.906
Dyslipidemia	303 (50.3)	45 (60.0)	73 (67.0)	79 (52.3)	106 (39.7)	<0.001
Ischemic heart disease	296 (49.2)	42 (56.0)	72 (66.1)	83 (55.0)	99 (37.1)	<0.001
Cardiomyopathy	110 (18.3)	12 (16.0)	10 (9.2)	26 (17.2)	62 (23.2)	0.013
Atrial fibrillation	249 (41.4)	5 (6.7)	20 (18.3)	45 (29.8)	179 (67.0)	<0.001
Echocardiography						
LVDd, mm	49.3 (6.7)	48.3 (4.9)	48.8 (5.9)	49.0 (7.3)	50.0 (7.1)	0.115
LVDs, mm	32.1 (6.5)	30.6 (5.1)	31.6 (5.8)	31.7 (6.6)	33.1 (6.8)	0.008
LVEF, %	63.7 (8.8)	66.3 (8.5)	64.4 (8.1)	63.7 (9.1)	62.8 (8.9)	0.016
LAD, mm	42.2 (8.3)	37.4 (5.2)	38.5 (5.1)	41.5 (9.1)	45.5 (8.3)	<0.001
E/A	0.94 (0.49)	0.91 (0.27)	0.87 (0.29)	0.93 (0.49)	1.04 (0.70)	0.122
Laboratory values						
eGFR, mL/min per 1.73 m^2	65.7 (18.6)	73.6 (16.4)	69.3 (17.5)	67.8 (18.3)	60.8 (18.6)	<0.001
Hemoglobin, g/L	13.7 (1.7)	14.3 (1.3)	14.0 (1.3)	13.9 (1.5)	13.4 (1.9)	<0.001
Hemoglobin A_{1c}, %	5.88 (0.87)	5.9 (0.96)	5.81 (0.72)	5.90 (0.94)	5.88 (0.86)	0.776
NT-proBNP, pg/mL	255 (103–655)	36 (24–43)	92 (74–105)	198 (162, 247)	752 (500–1140)	NA
GDF15, pg/mL	1179 (849–1768)	927 (613–1157)	998 (806–1453)	1100 (783, 1614)	1457 (1028–2219)	<0.001
hs-TnT, pg/mL	10 (7–16)	6 (5–9)	8 (6–12)	10 (6–14)	14 (9.5–20)	<0.001
CRP, pg/mL	702 (315–1795)	673 (297–1255)	605 (302–1290)	573 (272–1725)	879 (403–2270)	0.003
Medications, n (%)						
Olmesartan (study drug)	306 (50.8)	40 (53.3)	53 (48.6)	72 (47.7)	141 (52.8)	0.701
ACEi	477 (79.2)	63 (84.0)	79 (72.5)	118 (78.1)	217 (81.3)	0.184
β Bblocker	392 (65.1)	39 (52.0)	64 (58.7)	98 (64.9)	191 (71.5)	0.006
Diuretics	272 (45.2)	21 (28.0)	32 (29.4)	55 (36.4)	164 (61.4)	<0.001

The NT-proBNP 55 to 125 pg/mL group includes patients with NT-proBNP >55 and <125 pg/mL, and the NT-proBNP 125 to 300 pg/mL group includes patients with NT-proBNP ≥125 and <300 pg/mL. ACEi indicates angiotensin-converting enzyme inhibitor; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GDF15, growth differentiating factor-15; hs-TnT, high-sensitivity troponin T; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

frequent use of β blockers and diuretics (Table). Cardiac abnormalities were milder, with higher LVEF and subtle elevations in other biomarkers, including GDF15, hs-TnT, and CRP. Patients with NT-proBNP between 125 and 300 pg/mL at baseline were younger than those with NT-proBNP ≥300 pg/mL but were older than those with NT-proBNP <125 pg/mL. Cardiac abnormalities in left ventricular and left atrial dimensions were more modest compared with those with NT-proBNP ≥300 pg/mL. Renal function was also preserved in those with NT-proBNP between 125 and 300 pg/mL at baseline. Across the NT-proBNP groups (≤55, 55–125, and 125–300 pg/mL), there was a gradual increase in the incidence and risk of the composite outcome of HF hospitalization and all-cause death (Figure 1). The same findings were observed when adjusted for established covariates of NT-proBNP in patients with HFpEF. However, these risks remained significantly lower than those in patients with NT-proBNP ≥300 pg/mL.



	Number of patients	Number of events (event rate, per 100 person-years)	Unadjusted model			Adjusted model		
			HR	95% CI	p-value	HR	95% CI	p-value
≤55 pg/mL	75	12 (1.56)	0.17	0.09-0.30	<0.001	0.25	0.14-0.45	<0.001
55-125 pg/mL	109	20 (1.84)	0.20	0.12-0.32	<0.001	0.23	0.14-0.37	<0.001
125-300 pg/mL	151	66 (5.15)	0.56	0.42-0.75	<0.001	0.62	0.47-0.83	0.001
≥300 pg/mL	267	164 (8.95)	Ref			Ref		

Figure 1. Cumulative incidence and the risk of heart failure hospitalization or all-cause death across NT-proBNP groups at baseline.

HR indicates hazard ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Temporal Change in NT-proBNP

NT-proBNP concentrations for 3 years were available from 471 (78.2%) patients with HFpEF. In overall patients with HFpEF, the median concentration of NT-proBNP increased from 255 (IQR, 103–655) at baseline to 267.4 (IQR, 101–733) pg/mL at 3 years (P<0.001). Median NT-proBNP levels at 3 years were 50.9 (IQR, 26.7–71.8), 111.7 (IQR, 67.9–180.0), 219.4 (IQR, 126.0–366.4), and 802.1 (IQR, 507.9–1348.5) pg/mL in the groups of NT-proBNP ≤55, 55–125, 125–300, and ≥300 pg/mL at baseline, respectively. The temporal changes in NT-proBNP levels in the 4 groups from baseline to 3 years are graphically illustrated in Figure 2. Among 471 patients with HFpEF, 228 (48.4%) had NT-proBNP <300 pg/mL at both baseline and 3 years (Figure 3, blue), and 167 (35.5%) had NT-proBNP ≥300 pg/mL at both baseline and 3 years (Figure 3, red). Conversely, 24 (5.1%) patients experienced a decline in NT-proBNP to <300 pg/mL (Figure 3, green; ie, improved), while 52 (11.0%) patients experienced an increase in NT-proBNP to ≥300 pg/mL at 3 years (Figure 3, yellow; ie, worsened). Notably, 1 in 3 patients with NT-proBNP 125 to 300 pg/mL at baseline had increased NT-proBNP to ≥300 pg/mL at 3 years (Figure 3, table cell with a shaded pattern).

Clinical Characteristics and Outcomes of the Worsened Group

No remarkable baseline characteristics were found for patients who experienced an increase in NT-proBNP to ≥300 pg/mL, except for slightly advanced age (mean, 66.1 years) compared with the groups of patients with NT-proBNP <300 pg/mL at 3 years (Table S1). Patients who experienced an increase in NT-proBNP to ≥300 pg/mL (worsened group) demonstrated a significant dilation of LV end-systolic dimension from baseline (absolute mean change, 1.71±5.27 mm) and a reduction in LVEF from baseline (absolute mean change −3.75±10.51%) (Figure 4 and Table S2). They also had a significant increase in GDF15 and hs-TnT from baseline (Figure S2). A statistically significant decrease in the use of angiotensin-converting enzyme inhibitors was present in patient groups with persistently low and persistently high NT-proBNP (Figure S3). Over the median study period of 7.5 years from the 3-year visit, 26 composite events occurred in patients who experienced an increase in NT-proBNP to ≥300 pg/mL at 3 years (Figure 5). Notably, their event rate was similar to that of patients with persistently elevated NT-proBNP ≥300 pg/mL (10.23 versus 10.43 per 100 person-years). The risk of composite end point for patients with a decline

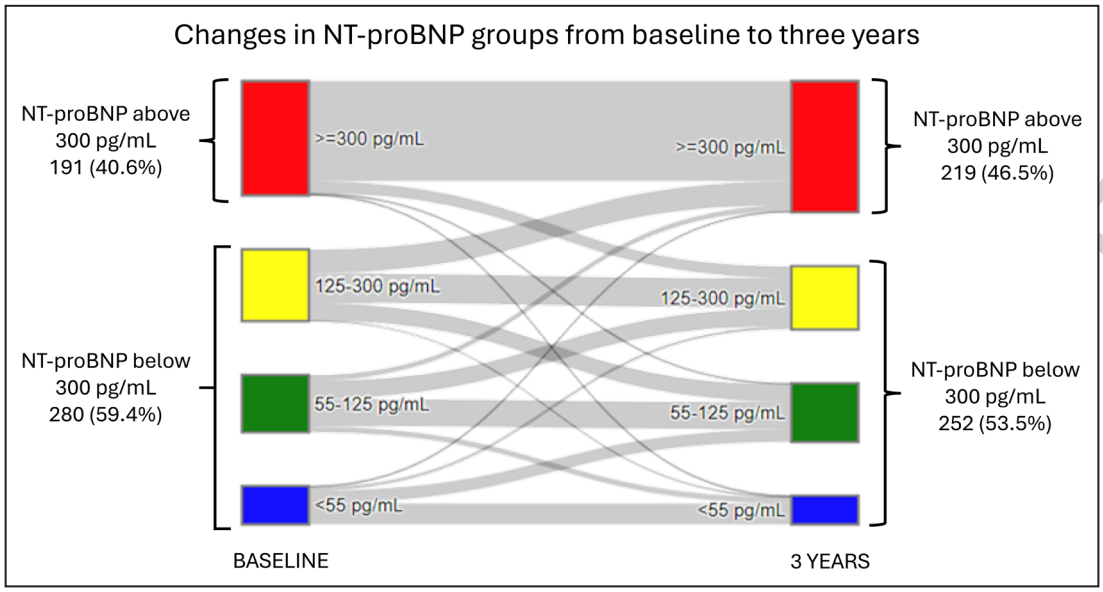


Figure 2. Change in NT-proBNP groups from baseline to 3 years.
NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

in NT-proBNP to <300 pg/mL (improved group) and an increase in NT-proBNP to ≥300 pg/mL (worsened group), was not different from that of those with NT-proBNP persistently ≥300 pg/mL (adjusted hazard ratios, 0.92 [95% CI, 0.47–1.81] and 1.08 [95% CI, 0.69–1.69], respectively; Figure 5).

DISCUSSION

In relatively young and stable patients with HFpEF from a Japanese chronic HF trial, we found that more than half of patients had NT-proBNP levels <300 pg/mL. Patients with NT-proBNP <300 pg/mL were younger,

NT-proBNP at BASELINE	NT-proBNP at 3 YEARS: ≤55 pg/mL	55-125 pg/mL	125-300 pg/mL	≥300 pg/mL
≤55 pg/mL	35 (54.7%)	21 (32.8%)	6 (9.4%)	2 (3.1%)
55-125 pg/mL	10 (10.4%)	46 (47.9%)	30 (31.9%)	10 (10.4%)
125-300 pg/mL	1 (0.8%)	29 (24.2%)	50 (41.7%)	40 (33.3%)
≥300 pg/mL	2 (1.0%)	2 (1.0%)	20 (10.5%)	167 (87.4%)

Persistently below 300 pg/mL
Worsened
Improved
Persistently above 300 pg/mL

Figure 3. Number of patients in each transitional group of NT-proBNP levels.
The width of the rows and columns of baseline and 3-year NT-proBNP groups is proportional to the number of patients at each visit. The frequencies presented in the parentheses correspond to the total number of patients in each row. The table cell with a dotted pattern indicates patients with mild elevation in NT-proBNP at baseline (125–300 pg/mL) who had an increase in NT-proBNP to ≥300 pg/mL at 3 years. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

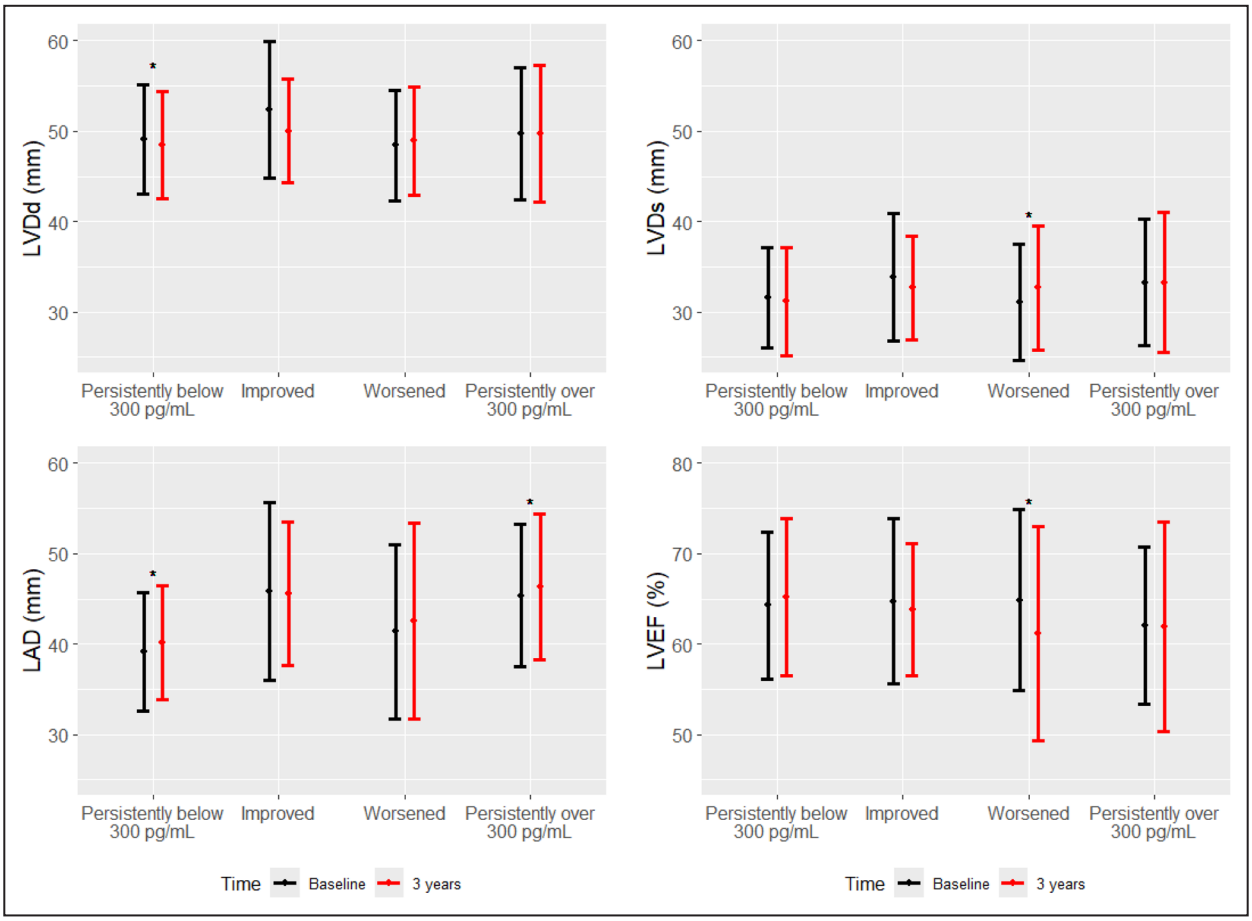


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Figure 4. Changes in echocardiographic parameters from baseline to 3 years across the transitional groups of NT-proBNP.

*P<0.05 for baseline versus 3 years. LAD indicates left atrial dimension; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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had higher body mass index, and were more likely to have dyslipidemia and ischemic heart disease compared with those with NT-proBNP ≥300 pg/mL. While these patients showed milder cardiac abnormalities and a lower risk of HF hospitalization or death, one third of those with NT-proBNP 125 to 300 pg/mL progressed to NT-proBNP ≥300 pg/mL at 3 years, accompanied by left ventricular dilation. Importantly, their subsequent risk of adverse outcomes was comparable to those with persistently elevated NT-proBNP.

While NT-proBNP ≥300 pg/mL serves as a good cutoff value to exclude definitive HF,[13–15] closer attention has been given to patients with HFpEF and marginal elevation in NPs. Verbrugge et al described the hemodynamic characteristics of patients with HFpEF and normal NP levels (defined as NT-proBNP <125 pg/mL) as those with better diastolic function, smaller left atrial volume, preserved right ventricular function, and less secondary valve regurgitation compared with high NP HFpEFs.[9] Despite milder cardiac abnormalities, they emphasized that normal NP HFpEFs are at increased risk of morbidity and death compared with controls without HF. Even taking into account biological characteristics, such as relatively younger age (66 versus 79 years), male predominance (70% versus 47%), and Asian ethnicity, compared with those reported in the KaRen (Karolinska–Rennes) HFpEF cohort,[16] all of which may have contributed to lower NT-proBNP levels, the striking finding that 30% of patients with HFpEF in the present study had NT-proBNP <125 pg/mL highlights the frequent encounter of HFpEF with normal NP levels in clinical practice.

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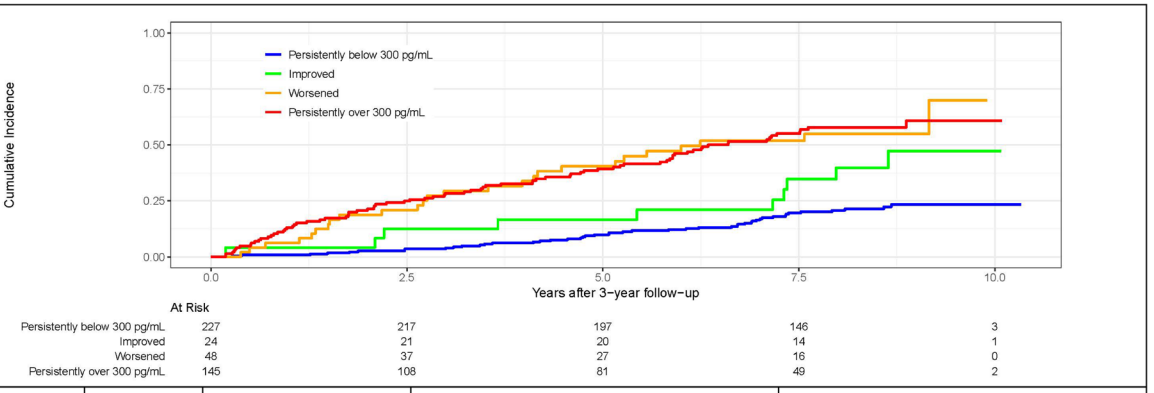
Patients with HFpEF, especially those with obesity, are well known for lower NP levels.[17] Bachmann et al identified a higher body mass index as the strongest predictor of lower BNP levels in patients hospitalized for HF, followed by younger age, higher LVEF, and lower creatinine.[18] While the mechanism underlying lower NP levels in individuals with obesity remains unclear, proposed explanations include impaired NP production due to insulin resistance and increased NP clearance via upregulated NP clearance receptors.[19]



	Number of patients	Number of events (event rate, per 100 person-years)	Unadjusted model			Adjusted model		
			HR	95% CI	p-value	HR	95% CI	p-value
Persistently below 300 pg/mL	227	47 (2.75)	0.26	0.18-0.37	<0.001	0.37	0.23-0.49	<0.001
Improved	24	10 (5.86)	0.55	0.28-1.05	0.072	0.92	0.47-1.81	0.809
Worsened	48	26 (10.23)	0.98	0.63-1.52	0.916	1.08	0.69-1.69	0.736
Persistently over 300 pg/mL	145	80 (10.43)	Ref			Ref		

Figure 5. The cumulative incidence of heart failure hospitalization and all-cause death after 3 years across transitional groups of NT-proBNP.

The adjusted model includes age, sex, body mass index, New York Heart Association class III, diabetes, and estimated glomerular filtration rate at baseline for multivariable adjustments. HR indicates hazard ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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In the same study, whole-exome sequencing of 9 patients with low BNP levels despite HF and/or severe cardiac dysfunction revealed potential loss-of-function variants in the NP clearance receptor gene *NPR3* in 2 individuals, suggesting a genetic contribution to NP regulation as well.

Patients with mild elevations in NP levels are both common and clinically significant. A study of 490 patients hospitalized for acute or worsening chronic HF found that 22% of those with HFpEF had BNP ≤200 pg/mL.[20] Similarly, our analysis showed that more than half of patients with stable HFpEF had NT-proBNP <300 pg/mL, with 25% classified as having mild elevations (125–300 pg/mL). These patients often exhibit milder cardiac abnormalities and better outcomes compared with those with overtly elevated NT-proBNP levels (≥300 pg/mL), which may lead to poor clinical attention. However, progression of HF was noted in one third of patients with preclinically elevated NT-proBNP levels, who developed overt elevations over 3 years alongside cardiac deterioration, highlighting the need for greater vigilance.

Notably, the shockingly overlapping incident curves and an equivalently heightened risk of HF hospitalization between patients with increased (over 3 years) and persistently elevated NT-proBNP underscore the importance of reconsidering how patients with mild elevations in NT-proBNP at baseline are monitored and managed. Careful follow-up and early interventions may be warranted, as evidence points to the potential for significant declines in cardiac function and morphology over time. These findings suggest that patients with preclinical NT-proBNP elevations represent a critical group within HFpEF that requires more focused attention in both clinical care and research.

Some existing literature suggests the potential benefit of renin–angiotensin system inhibitors such as irbesartan or spironolactone in HFpEF with lower NP.[21,22] Meanwhile, subgroup analysis of the 2 trials of sodium–glucose cotransporter 2 inhibitor implied its consistent benefit across a wide range of NT-proBNP on the basis of the nonsignificant interaction terms, even though both trials included patients with NT-proBNP >300 pg/mL.[23,24] Nevertheless, it is important to note that the interpretation of the interaction terms and subgroup analysis should be carefully narrated by the trial designs (subgroup analysis should be prespecified), trial results (overall results being preferably positive), and statistical power (an adequate number of targeted patients should be included).[25] Dedicated prospective studies are needed to determine the optimal treatment strategies for unexpectedly lower NP HFpEFs.

Several limitations should be mentioned for the present study. First, the findings are based on data from a clinical trial in Japan, studying patients with HFpEF with baseline and 3-year measurements

of NT-proBNP, which may limit their applicability to populations of different races and clinical settings. Second, cardiac abnormalities in the patients might have been underassessed due to the limited echocardiographic data collected during the trial. Third, misclassification bias due to inherent measurement errors in NT-proBNP and/or LVEF cannot be negated, as the SUPPORT trial was a multicenter study in which the differences in laboratories, utility vendors, and the technical skills of scientists/sonographers may influence biological measurements. Nonetheless, we perceive that the impact of such measurement errors is minimal and nonsystematic, given that these measurements were performed as part of routine clinical care. Thus, longitudinal collection of such measurements based on the same assay system would mitigate within-patient variabilities over time. Fourth, the relatively lower event rates in patients with HFpEF and lower NT-proBNP levels may have reduced the statistical power of the analysis. Although the PROBE approach was taken in the SUPPORT trial, the unblinding bias introduced by the open-label condition may have influenced the event rate. Fifth, it is important to note that the present findings apply to patients with diagnosed HF, despite the NT-proBNP cutoff values used in the study being primarily used for the diagnosis of HF. Furthermore, given the unavailability of the history of HF (ie, duration since HF diagnosis and prior data on LVEF), the study may include patients with a wide range of HF severity, including those with improved systolic function before the study enrollment. Sixth, the relatively younger age in the present study compared with the typical HFpEF population warrants caution in the interpretation of the study results. Given the unavailability of measures of lung and day-to-day function, the potential influence of these factors on NT-proBNP measurements was not addressable in the present study. Thus, residual confounding may be present. Finally, any multiplicity adjustments were not made in our analysis, given the explorative nature of the present study. Therefore, we acknowledge that our findings are hypothesis generating and require further corroboration in future studies.

Although tangible evidence of HFpEF beyond LVEF was not available at the time of enrollment, we leveraged the study to explore the long-term trend of NT-proBNP levels in patients with potential HFpEF. Relatively long follow-up data have offered an exceptional opportunity to understand the relationship between the change in NT-proBNP in the first 3 years and outcomes occurring beyond the third year in patients without overt NP elevation at baseline. A slow but steady aggravation over 3 years should raise awareness to exercise caution and follow them carefully. Further investigation on predictors of patients with HFpEF with an expected increase in NT-proBNP may be warranted.

CONCLUSIONS

In patients with hypertension and chronic HFpEF enrolled in the SUPPORT trial, more than half of them had NT-proBNP <300 pg/mL at baseline, with fewer comorbidities and better outcomes than those with NT-proBNP ≥300 pg/mL. However, patients with lower NT-proBNP, including those with mild elevation between 125 and 300 pg/mL, are at increased risk of progression to overt elevations and worse outcomes, demonstrating the importance of closer monitoring and follow-up of those patients.

APPENDIX

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Disclosures

None.

Supplemental Material

Figures S1–S3
Data S1

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