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Low Natriuretic Peptide Levels and Outcomes in Patients With Heart Failure and Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Although some patients with heart failure (HF) with mildly reduced/preserved ejection fraction have low natriuretic peptide levels, there are no large-scale systematic studies of how common these individuals are or what happens to them.

OBJECTIVES The purpose of this study was to examine the proportion of patients in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial with an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level <125 pg/mL, their clinical characteristics, and outcomes.

METHODS I-PRESERVE enrolled patients with symptomatic HF and a LVEF \geq 45% but who did not have NT-proBNP or body mass index inclusion/exclusion criteria. Baseline NT-proBNP was measured after enrollment but not reported to investigators. The primary outcome in this analysis was the composite of cardiovascular death or HF hospitalization.

RESULTS Overall, 808 of 3,480 patients (23.2%) had NT-proBNP <125 pg/mL. Patients with a low NT-proBNP were younger (68.6 years vs 72.6 years; $P < 0.001$), were less often men (36.1% vs 40.9%; $P = 0.015$), and had a higher body mass index (48.4% vs 38.7% obese; $P < 0.001$) than those with a higher NT-proBNP level. Patients with a low NT-proBNP had less atrial fibrillation (8.5% vs 35.1%; $P < 0.001$), myocardial infarction, diabetes, chronic obstructive pulmonary disease, and anemia but better kidney function. Patients with a lower NT-proBNP level had less marked echocardiographic abnormalities and were less likely to experience cardiovascular death or HF hospitalization; adjusted HR: 0.35 (95% CI: 0.27-0.46; $P < 0.001$). However, health status was similarly impaired in patients with lower and higher NT-proBNP levels (median Minnesota Living with Heart Failure Questionnaire 43 vs 43; $P = 0.95$).

CONCLUSIONS Almost one-quarter of patients with HF with mildly reduced/preserved ejection fraction had a low NT-proBNP level. Although these patients have a favorable prognosis, compared to those with a high NT-proBNP level, they have similarly impaired health status which should be a target for treatment. (Irbesartan in Heart Failure With Preserved Systolic Function [I-PRESERVE]; [NCT00095238](https://clinicaltrials.gov/ct2/show/study/NCT00095238)) (J Am Coll Cardiol HF 2024; ■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****AF** = atrial fibrillation**AFL** = atrial flutter**HF** = heart failure**HFmrEF** = heart failure with mildly reduced ejection fraction**HFpEF** = heart failure with preserved ejection fraction**LVEF** = left ventricular ejection fraction**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**PCWP** = pulmonary capillary wedge pressure

Measurement of natriuretic peptides is helpful in the diagnostic work-up of patients with suspected heart failure (HF), and current guidelines specify a “rule out” threshold for N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 125 pg/mL, ie, they stipulate that a diagnosis of heart failure is unlikely in patients with a level below this cutoff.¹⁻³ However, this biomarker criterion has been controversial because it has been shown that some patients with heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) may have an NT-proBNP level

below this value, especially in individuals with obesity or when NT-proBNP is measured after diuretic therapy has been started.⁴⁻⁷ What proportion of patients with HFmrEF/HFpEF have a low NT-proBNP has not been evaluated in any large cohort where patients were not enrolled based on any natriuretic peptide criterion.⁶⁻⁸ Similarly, how the clinical characteristics and outcomes of these individuals compare to patients with a higher NT-proBNP level is poorly studied. The I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction; [NCT00095238](#)) trial offers a unique opportunity to examine these questions because patients were enrolled in that trial based on a clinical diagnosis of HF, with no natriuretic peptide-based enrollment criterion. Indeed, at the time this trial enrolled patients (2002-2005), routine measurement of natriuretic peptides was uncommon. However, as part of the trial protocol, most patients had a measurement of NT-proBNP in a blood sample collected at baseline (these samples were sent for subsequent assay in a central laboratory and investigators were unaware of the results). Moreover, unlike more recent trials, patients with a high body mass index were not excluded from I-PRESERVE. Therefore, we investigated the proportion of patients with an NT-proBNP <125 pg/mL in the I-PRESERVE trial, their clinical characteristics, and outcomes.

METHODS

The design, baseline characteristics, and results of I-PRESERVE are published.⁹⁻¹¹ Briefly, 4,128 patients aged ≥ 60 years with a left ventricular ejection fraction (LVEF) $\geq 45\%$, signs and symptoms of HF, and corroborating evidence (radiological evidence of pulmonary congestion, electrocardiographic left ventricular hypertrophy or left bundle branch block, or echocardiographic left atrial enlargement of left ventricular

hypertrophy) were randomized to 300 mg once daily irbesartan or placebo ([Supplemental Table 1](#)). Patients in NYHA functional classes II to IV were eligible, but those in NYHA functional class II were required to have had a hospitalization for HF within the previous 6 months. Patients with a plasma creatinine level of more than 2.5 mg/dL (221 $\mu\text{mol/L}$) were excluded. Ethics committees at each participating institute approved the trial, and all patients provided written informed consent. The mean follow-up was of 49.5 months. Irbesartan had no significant effect on the primary composite outcome of death from any cause or hospitalization for a cardiovascular cause, or on any of the prespecified secondary endpoints.

To compare the characteristics and outcomes between I-PRESERVE and other trials that applied NT-proBNP as an inclusion criteria, we analyzed the PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction; [NCT01920711](#)) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; [NCT03619213](#)) data sets.¹²⁻¹⁶ The design, baseline characteristics, and results of PARAGON-HF and DELIVER are published, and the design of these trials is summarized in [Supplemental Table 1](#).¹²⁻¹⁶

MEASUREMENT OF NT-proBNP. NT-proBNP was measured during the trial in a central laboratory using a sandwich immunoassay on an Elecsys 2010 platform (Roche Diagnostics). Patients without NT-proBNP at baseline were excluded from the analysis (n = 648). We divided patients according to their NT-proBNP <125 and ≥ 125 pg/mL, which is the cutoff proposed in the guideline and the consensus recommendation for diagnosis of HFpEF.^{1,17}

ECHOCARDIOGRAPHIC SUBSTUDY. In I-PRESERVE, the echocardiographic substudy was only conducted in patients in normal sinus rhythm to ensure good image quality. Echocardiography was performed using a standardized protocol and methods as described by the American Association of Echocardiography at the time.¹⁸⁻²¹ Left ventricular volume was calculated using the area of discs method.¹⁸⁻²¹ Peak transmitral early diastolic velocity (E), late diastolic velocity (A), and myocardial long-axis lengthening velocity (E') were obtained. Right ventricular systolic pressure was estimated using peak tricuspid regurgitant velocity (V) as $4(V^2) + 10$ mm Hg. All echocardiograms were analyzed at the echocardiography core laboratory at the University of Maryland.

STUDY OUTCOMES AND DEFINITION. The original primary outcome in I-PRESERVE was the time to a composite of death from any cause or hospitalization for a protocol-specified cardiovascular cause. To compare with other clinical trials, we analyzed the composite of cardiovascular death or HF hospitalization as the primary outcome in the present study. In addition, time to cardiovascular death, HF hospitalization, and all-cause death were evaluated. In each trial, all deaths and HF hospitalizations were adjudicated according to prespecified criteria by members of an independent clinical events committee who were unaware of study group assignments.

STATISTICAL ANALYSIS. The distributions of NT-proBNP for patients with and without atrial fibrillation (AF) (including atrial flutter [AFL]) on the baseline electrocardiography for each trial and those of body mass index were evaluated. The association between NT-proBNP and body mass index was analyzed using a regression model with body mass index modelled as a restricted cubic spline with 5 knots. Baseline characteristics and echocardiographic parameters were summarized according to NT-proBNP level (≥ 125 pg/mL vs NT-proBNP < 125 pg/mL) as mean \pm SD or median (IQR) for continuous variables and counts and percentages for categorical variables. Differences in baseline characteristics were tested using the Fisher exact or chi-square test for binary or categorical variables, the Student's *t*-test for normally distributed continuous variables, and the Wilcoxon rank sum test for non-normally distributed continuous variables, respectively. The total score, physical dimension, and emotional dimension of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) at baseline were compared between patients with NT-proBNP ≥ 125 and < 125 pg/mL using the Wilcoxon rank sum test, and the score for each of the 21 questions of the MLHFQ were compared using ordinal logistic regression models.²² Normal ranges regarding echocardiography parameters were obtained from the echocardiographic core laboratory and the American Society of Echocardiography at the time I-PRESERVE was conducted.^{19,20,23-25}

To evaluate the difference in outcomes according to patients with NT-proBNP ≥ 125 pg/mL and < 125 pg/mL, Cox proportional-hazards models were used to compute HRs with 95% CIs with those with NT-proBNP < 125 pg/mL as a reference regardless of randomized treatment, adjusted for treatment assignment in model 1, and adjusted for treatment assignment, age, sex, region, systolic blood pressure, heart rate, body mass index, NYHA functional class,

hospitalization for HF within previous 6 months, LVEF, history of myocardial infarction, history of hypertension, history of diabetes, AF or AFL in electrocardiography, and estimated glomerular filtration rate in model 2. Complete case analysis for the Cox proportional hazards models adjusted for covariables was conducted, because the percentage of missing data was not substantial (1.2%). Kaplan-Meier outcomes curves were plotted separately for patients with low and high NT-proBNP assigned to the irbesartan or placebo.

As the sensitivity analyses, patient characteristics and outcomes according to NT-proBNP categories were evaluated in patients with LVEF $\geq 50\%$.

To compare patients in I-PRESERVE with those in other trials, the characteristics and echocardiographic findings of patients with an NT-proBNP > 300 pg/mL if not AF (or > 600 pg/mL if AF) in I-PRESERVE and those in PARAGON-HF and DELIVER are shown, and the number of events and incidence rate (per 100 person-years) were estimated among patients in the placebo group with different cutoffs for NT-proBNP in I-PRESERVE, the valsartan group in PARAGON-HF, and the placebo group in DELIVER. For this analysis, only DELIVER patients with LVEF $\geq 45\%$ were included. There was no echocardiographic substudy in DELIVER.

All analyses were performed with complete case analysis and conducted using STATA version 17.0.

RESULTS

DISTRIBUTION OF NT-proBNP AT BASELINE AND BODY MASS INDEX IN I-PRESERVE COMPARED WITH OTHER HFmrEF/HFpEF TRIALS. The median baseline NT-proBNP in I-PRESERVE overall was 339 (Q1-Q3: 134-964) compared with 911 (Q1-Q3: 464-1,613) in PARAGON-HF and 990 (Q1-Q3: 617-1,690) in DELIVER. In patients without AF, the median baseline NT-proBNP in I-PRESERVE (82.8%) was 256 (Q1-Q3: 113-618) compared with 599 (Q1-Q3: 380-1,055) in PARAGON-HF (67.5%) and 690 (Q1-Q3: 454-1,199) in DELIVER (56.1%). The distribution of NT-proBNP for patients with and without AF at baseline in I-PRESERVE, PARAGON-HF, and DELIVER is shown in [Supplemental Figure 1](#).

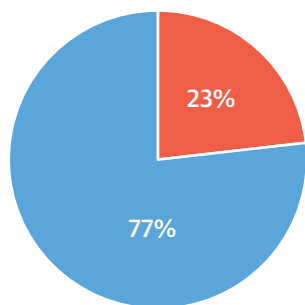
The median body mass index in I-PRESERVE was 28.8 kg/m², and the proportions of patients with a very high body mass index, which met the exclusion criteria in PARAGON-HF (> 40 kg/m²) and DELIVER (> 50 kg/m²), were 3.9% and 0.2%, respectively ([Supplemental Figure 2](#)).

CENTRAL ILLUSTRATION Heart Failure With Preserved Ejection Fraction and Low NT-proBNP Levels

I-PRESERVE: N = 3,480

Inclusion

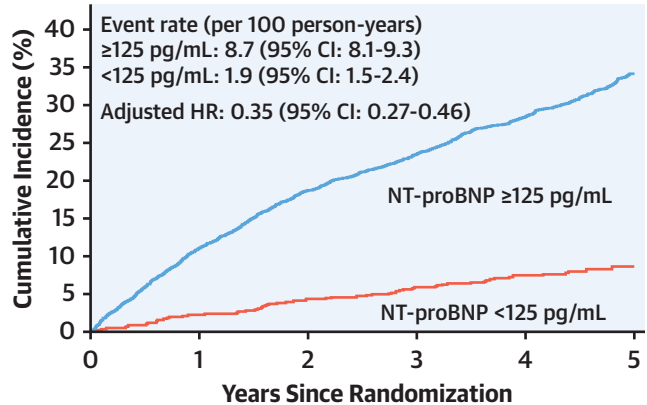
Age ≥ 60 years, LVEF $\geq 45\%$
 NYHA functional class III-IV or II-IV
 with HF
 Hospitalization history within 6 months
 Current signs and symptoms of HF



■ NT-proBNP <125 pg/mL
 ■ NT-proBNP ≥ 125 pg/mL

Characteristics of Patients With Low NT-proBNP Levels

Younger, more often female
 Higher body mass index
 Less evidence of congestion
 Less AF, MI history, DM, COPD, anemia
 More hypertension
 Better kidney function
 Fewer ECG/echocardiographic abnormalities
 Similarly depressed health status

Cardiovascular Death or HF Hospitalization

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The left lower panel shows the proportion of patients with an NT-proBNP level <125 and ≥ 125 pg/mL. The right lower panel shows the difference in the outcome on cardiovascular death or HF hospitalization according to patients with NT-proBNP <125 and ≥ 125 pg/mL. HR was adjusted for treatment assignment, age, sex, region, systolic blood pressure, heart rate, body mass index, NYHA functional class, hospitalization for HF within previous 6 months, LVEF, history of MI, history of hypertension, history of DM, AF or atrial flutter on an electrocardiogram, and estimated glomerular filtration rate. AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ECG = electrocardiography; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

PATIENT CHARACTERISTICS ACCORDING TO BASELINE NT-proBNP LEVEL.

In I-PRESERVE, of 3,480 patients included, 808 patients (23.2%) had NT-proBNP <125 pg/mL and 2,672 patients (76.8%) had NT-proBNP ≥ 125 pg/mL (Central Illustration). Patients with NT-proBNP <125 and ≥ 125 pg/mL had different baseline characteristics, including demographics, HF characteristics, and comorbidities (Table 1). Patients with NT-proBNP <125 pg/mL were younger (68.6 years vs 72.6 years), less often male (36.1% vs 40.9%), and had a higher body mass index (48.4% vs 38.7% obese [body mass index ≥ 30 kg/m²]) compared with those with NT-proBNP ≥ 125 pg/mL. The association

between body mass index and NT-proBNP at baseline is shown in Supplemental Figure 3.

Congestion markers, including elevated jugular venous pressure, rales, and pulmonary congestion on the chest x-ray, were less prevalent in patients with NT-proBNP <125 pg/mL. LVEF was slightly higher in patients with a low NT-proBNP. Regarding comorbidities, patients with NT-proBNP <125 pg/mL were less likely to have AF (8.5% vs 35.1%), myocardial infarction, diabetes mellitus, stroke, and chronic obstructive pulmonary disease or asthma. They also had markedly better kidney function and less anemia than patients with an NT-proBNP ≥ 125 pg/mL. By

TABLE 1 Patient Characteristics According to NT-proBNP Categories

	Overall (N = 3,480)	NT-proBNP <125 pg/mL (n = 808)	NT-proBNP ≥125 pg/mL (n = 2,672)	P Value
Age, y	71.7 ± 6.9	68.6 ± 6.1	72.6 ± 6.9	<0.001
Age group				<0.001
<70 y	1,422 (40.9)	483 (59.8)	939 (35.1)	
≥70 y	2,058 (59.1)	325 (40.2)	1,733 (64.9)	
Region				<0.001
North America	283 (8.1)	42 (5.2)	241 (9.0)	
Latin and Central America	622 (17.9)	176 (21.8)	446 (16.7)	
Western Europe	1,207 (34.7)	239 (29.6)	968 (36.2)	
Central and Eastern Europe (including Russia)	1,292 (37.1)	339 (42.0)	953 (35.7)	
Asia-Pacific, and other	76 (2.2)	12 (1.5)	64 (2.4)	
Male	1,385 (39.8)	292 (36.1)	1,093 (40.9)	0.015
Race				0.51
White	3,263 (93.8)	758 (93.8)	2,505 (93.8)	
Black	62 (1.8)	15 (1.9)	47 (1.8)	
Asian	32 (0.9)	4 (0.5)	28 (1.0)	
Others	123 (3.5)	31 (3.8)	92 (3.4)	
Systolic blood pressure, mm Hg	136 ± 15	137 ± 14	136 ± 15	0.23
Diastolic blood pressure, mm Hg	79 ± 9	80 ± 8	78 ± 9	<0.001
Heart rate, beats/min	71 ± 10	71 ± 9	71 ± 11	0.76
In patients without AF on ECG, beats/min	70 ± 10	71 ± 9	70 ± 10	0.006
In patients with AF on ECG, beats/min	76 ± 12	74 ± 7	76 ± 12	0.44
Body mass index, kg/m ²	29.6 ± 5.2	30.4 ± 5.0	29.3 ± 5.2	<0.001
Weight category ³				<0.001
Underweight	16 (0.5)	1 (0.1)	15 (0.6)	
Normal	570 (16.4)	83 (10.3)	487 (18.3)	
Overweight	1,461 (42.1)	333 (41.2)	1,128 (42.4)	
Obese	1,421 (41.0)	391 (48.4)	1,030 (38.7)	
Current smoker	623 (17.9)	145 (17.9)	478 (17.9)	0.97
HF characteristics				
Left ventricular hypertrophy or left atrial enlargement on echocardiography as inclusion criteria	3,009 (86.5)	703 (87.0)	2,306 (86.3)	0.61
NYHA functional class				0.012
II	711 (20.4)	139 (17.2)	572 (21.4)	
III	2,678 (77.0)	653 (80.8)	2,025 (75.8)	
IV	90 (2.6)	16 (2.0)	74 (2.8)	
Time from diagnosis of HF, d	404 (93-1251)	413 (117-1208)	390 (89-1267)	0.58
Hospitalization for HF in prior 6 mo	1,508 (43.3)	261 (32.3)	1,247 (46.7)	<0.001
Investigator reported cause of HF				<0.001
Ischemic	885 (25.4)	141 (17.5)	744 (27.8)	
Hypertension	2,217 (63.7)	609 (75.4)	1,608 (60.2)	
Valvular heart disease	43 (1.2)	1 (0.1)	42 (1.6)	
Others	335 (9.6)	57 (7.1)	278 (10.4)	
LVEF, %	59.5 ± 9.2	61.3 ± 8.5	59.0 ± 9.3	<0.001
MLHFQ				
Total MLHFQ score	43 (28-59)	43 (29-58)	43 (28-59)	0.95
Physical dimension	22 (15-29)	22 (15-28)	23 (15-29)	0.60
Emotional dimension	8 (3-13)	8 (4-13)	8 (3-13)	0.91
Markers of congestion				
Pulmonary congestion on chest x-ray	1,356 (40.3)	254 (32.2)	1,102 (42.8)	<0.001
Peripheral edema				0.14
None	1,564 (45.0)	367 (45.4)	1,197 (44.8)	
Trace	1,082 (31.1)	267 (33.0)	815 (30.5)	
1+ to 2+	762 (21.9)	164 (20.3)	598 (22.4)	
3+ to 4+	69 (2.0)	10 (1.2)	59 (2.2)	

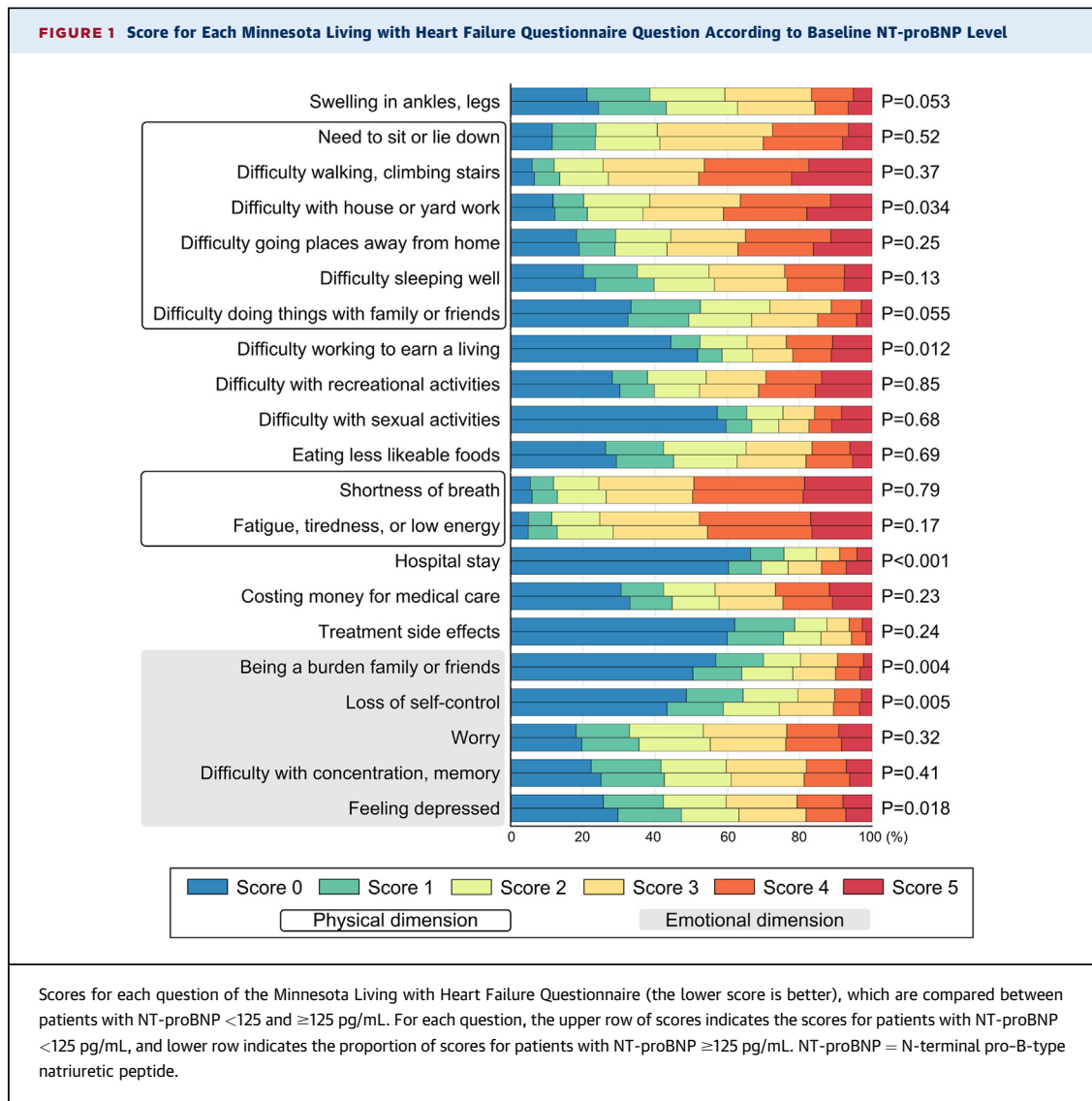
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TABLE 1 Continued

	Overall (N = 3,480)	NT-proBNP <125 pg/mL (n = 808)	NT-proBNP ≥125 pg/mL (n = 2,672)	P Value
Third heart sound	284 (8.2)	53 (6.6)	231 (8.7)	0.057
Elevated jugular venous pressure	296 (8.5)	40 (5.0)	256 (9.6)	<0.001
Rales				0.046
Clear	2,422 (69.7)	584 (72.3)	1,838 (68.9)	
Wheezing only	70 (2.0)	22 (2.7)	48 (1.8)	
Basilar rales	878 (25.3)	182 (22.5)	696 (26.1)	
Diffuse rales	107 (3.1)	20 (2.5)	87 (3.3)	
Liver enlargement	648 (18.7)	144 (17.9)	504 (18.9)	0.50
Comorbidities				
AF	1,008 (29.0)	69 (8.5)	939 (35.1)	<0.001
Myocardial infarction	839 (24.1)	99 (12.3)	740 (27.7)	<0.001
Angina pectoris	1,543 (44.3)	323 (40.0)	1,220 (45.7)	0.004
PCI or CABG	459 (13.2)	60 (7.4)	399 (14.9)	<0.001
Hypertension	3,084 (88.6)	737 (91.2)	2,347 (87.8)	0.008
Diabetes	963 (27.7)	198 (24.5)	765 (28.6)	0.022
Stroke or transient ischemic attack	334 (9.6)	59 (7.3)	275 (10.3)	0.011
Chronic obstructive pulmonary disease or asthma	317 (9.1)	57 (7.1)	260 (9.7)	0.021
ECG findings				
AF or atrial flutter	597 (17.2)	16 (2.0)	581 (21.7)	<0.001
QRS duration, ms	90 (80-100)	86 (80-100)	90 (80-104)	<0.001
Left bundle branch block	265 (8.1)	45 (5.7)	220 (8.9)	0.004
Right bundle branch block	243 (7.4)	50 (6.3)	193 (7.8)	0.16
Left ventricular hypertrophy on ECG	1,026 (31.3)	222 (27.9)	804 (32.4)	0.017
Laboratory data				
NT-proBNP, pg/mL	339 (134-964)	69 (43-96)	534 (256-1229)	<0.001
In patients without AF on ECG	256 (113-618)	69 (43-97)	401 (224-897)	<0.001
In patients with AF on ECG	1272 (757-2026)	62 (45-92)	1312 (814-2058)	<0.001
eGFR, mL/min/1.73 m ²	72 ± 22	82 ± 22	70 ± 22	<0.001
eGFR <60 mL/min/1.73 m ²	1,066 (30.8)	128 (15.9)	938 (35.4)	<0.001
Serum creatinine, μmol/L	89 ± 29	78 ± 27	92 ± 29	<0.001
Blood urea nitrogen, mmol/L	7.6 ± 3.3	6.6 ± 2.1	7.9 ± 3.6	<0.001
Albumin, g/dL	4.5 ± 1.7	4.2 ± 1.3	4.6 ± 1.8	<0.001
Serum sodium, mmol/L	140 ± 3	140 ± 3	140 ± 3	0.65
Hemoglobin, g/L	139 ± 19	142 ± 18	138 ± 20	<0.001
Anemia	437 (12.8)	47 (5.9)	390 (14.9)	<0.001
Drugs and interventions				
ACE inhibitor	896 (25.7)	178 (22.0)	718 (26.9)	0.006
Beta-blocker	2,053 (59.0)	418 (51.7)	1,635 (61.2)	<0.001
Spironolactone	531 (15.3)	96 (11.9)	435 (16.3)	0.002
Any diuretic	2,870 (82.5)	616 (76.2)	2,254 (84.4)	<0.001
Loop diuretic	1,808 (52.0)	289 (35.8)	1,519 (56.8)	<0.001
Calcium channel blocker	1,407 (40.4)	373 (46.2)	1,034 (38.7)	<0.001
Nitrate	922 (26.5)	166 (20.5)	756 (28.3)	<0.001
Digoxin	473 (13.6)	34 (4.2)	439 (16.4)	<0.001
Antiarrhythmic agent	298 (8.6)	42 (5.2)	256 (9.6)	<0.001
Anticoagulant agent	629 (18.1)	39 (4.8)	590 (22.1)	<0.001
In patients with AF on ECG	373 (62.5)	6 (37.5)	367 (63.2)	0.036
In patients with AF history	523 (51.9)	20 (29.0)	503 (53.6)	<0.001
Implantable cardioverter-defibrillator	9 (0.3)	1 (0.1)	8 (0.3)	0.69
Pacemaker	206 (5.9)	13 (1.6)	193 (7.2)	<0.001

Values are n (%), mean ± SD, or median (Q1-Q3). ^aUnderweight, body mass index <18.5 kg/m²; normal, body mass index 18.5-25.0 kg/m²; overweight, body mass index 25.0-30.0 kg/m²; and obese, body mass index ≥30 kg/m². Heart rate is missing in 3 cases; body mass index in 12 cases; current smoker and NYHA functional class in 1 case; time from diagnosis of heart failure (HF) in 4 cases; LVEF in 3 cases; Minnesota Living with Heart Failure Questionnaire (MLHFQ) score in 791 patients; pulmonary congestion in 118 cases; peripheral edema, third heart sound, elevated jugular venous pressure, and rales in 3 cases; liver enlargement in 10 cases; QRS duration in 211 cases; left bundle branch block and left ventricular hypertrophy on electrocardiography (ECG) in 206 cases; right bundle branch block in 210 cases; estimated glomerular filtration rate (eGFR) and serum creatinine in 23 cases; blood urea nitrogen, albumin, serum sodium in 24 cases; and hemoglobin in 65 cases.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention.



contrast, patients with NT-proBNP <125 pg/mL had a more frequent history of hypertension. Regarding medications, patients with NT-proBNP <125 pg/mL were treated with an angiotensin-converting enzyme inhibitor, beta-blocker, and spironolactone less frequently, but calcium-channel blockers more frequently, than participants with an NT-proBNP ≥125 pg/mL. Patient characteristics according to NT-proBNP categories among those assigned to irbesartan vs placebo and those aged <70 years vs ≥70 years were shown in [Supplemental Tables 2 and 3](#), respectively. In patients with LVEF ≥50%, similar characteristics according to NT-proBNP

categories were obtained, while the proportion of NT-proBNP <125 pg/mL was slightly higher at 25% ([Supplemental Table 4](#)).

MLHFQ ACCORDING TO BASELINE NT-proBNP LEVEL. Total MLHFQ score was similar in patients with a lower compared with higher NT-proBNP (43 [Q1-Q3: 29-58] vs 43 [Q1-Q3: 28-59]) ([Table 1](#)). The physical dimensions were also similar in each group. By contrast, across the emotional dimensions, those with a lower NT-proBNP had better scores for some questions (being a burden family or friend, and loss of self-control) but worse for the question about depression ([Figure 1](#)).

TABLE 2 Echocardiographic Findings According to NT-proBNP Categories

	Available Data	Total (N = 673)	NT-proBNP <125 pg/mL (n = 164)	NT-proBNP ≥125 pg/mL (n = 509)	P Value	Normal Range ^a
LV end diastolic diameter, cm	584	4.8 ± 0.6	4.7 ± 0.6	4.9 ± 0.6	<0.001	4.0-6.0
LV end-diastolic volume, mL, mL/m ²	526	95 ± 38, 50 ± 19	88 ± 36, 47 ± 17	97 ± 39, 51 ± 19	0.031 ^b	80-180, 40-90
LV end systolic diameter, cm	563	3.2 ± 0.7	3.0 ± 0.5	3.2 ± 0.7	<0.001	2.0-4.0
LV end-systolic volume, mL, mL/m ²	526	35 ± 19, 19 ± 10	30 ± 14, 16 ± 7	36 ± 20, 19 ± 10	0.001 ^b	25-50, 15-25
Interventricular septum thickness, cm	619	0.98 ± 0.16	0.94 ± 0.15	0.99 ± 0.16	0.001	0.8-0.9
LV wall posterior wall thickness, cm	621	0.92 ± 0.15	0.91 ± 0.14	0.93 ± 0.15	0.089	0.8-0.9
Mass, g, g/height ^{2.7}	577	164 ± 49, 43 ± 13	149 ± 44, 39 ± 10	169 ± 49, 44 ± 13	<0.001 ^b	80-140, 18-38
Relative wall thickness	581	0.39 ± 0.08	0.39 ± 0.08	0.38 ± 0.08	0.32	0.36-0.40
Mass/LV end-diastolic volume, g/mL	478	1.93 ± 0.79	1.82 ± 0.66	1.96 ± 0.82	0.12	1.25-1.75
LV ejection fraction, %	528	64 ± 9	66 ± 7	63 ± 10	0.002	55-75
Fractional shortening, %	554	34 ± 10	36 ± 9	34 ± 10	0.053	30-45
Stroke volume, mL	528	60 ± 24	58 ± 24	61 ± 24	0.38	50-70
MV peak e wave velocity, cm/s	652	78 ± 28	68 ± 18	82 ± 30	<0.001	40-90
MV peak a wave velocity, cm/s	591	82 ± 27	86 ± 20	80 ± 29	0.015	40-100
E/A	582	1.04 ± 0.75	0.81 ± 0.23	1.12 ± 0.85	<0.001	0.6-1.4
Lateral e', cm/s	477	9.1 ± 3.5	8.4 ± 2.4	9.3 ± 3.7	0.013	7.0-11.5
Septal e', cm/s	462	7.2 ± 2.9	6.8 ± 2.2	7.3 ± 3.1	0.11	5.0-11.0
E/e' lateral	470	9.8 ± 4.6	8.9 ± 3.0	10.1 ± 4.9	0.023	4.5-11.5
Left MV deceleration time, msec	650	216 ± 78	228 ± 78	212 ± 77	0.031	185-310
LA area, cm ² , cm ² /m ²	624	23 ± 6, 12 ± 3	20 ± 4, 11 ± 2	24 ± 6, 13 ± 3	<0.001 ^b	10-20, 5-10
RV systolic pressure, mm Hg	350	37 ± 13	31 ± 10	38 ± 13	<0.001	15-25

Values are mean ± SD. Body surface area was calculated by Du Bois formula: $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$. ^aFull range. ^bDifferences in LV end-diastolic volume index, LV end-systolic volume index, mass index, and LA index.
LA = left atrial; LV = left ventricular; MA = mitral annulus; MV = mitral valve; RV = right ventricular; other abbreviation as in Table 1.

ECHOCARDIOGRAPHIC FINDINGS ACCORDING TO BASELINE NT-proBNP LEVEL. Generally, patients with NT-proBNP <125 pg/mL had less marked echocardiographic abnormalities than those with NT-proBNP ≥125 pg/mL (Table 2). Left ventricular wall thickness and left ventricular mass were higher than normal in both groups, but the elevation was less in patients with NT-proBNP <125 pg/mL. Despite measurements only being made in patients in sinus rhythm, the left atrial area was increased from normal in both groups but was smaller in those with NT-proBNP <125 pg/mL than those with NT-proBNP ≥125 pg/mL. Both groups had elevated right ventricular systolic pressure but this pressure was lower in patients with an NT-proBNP <125 pg/mL.

EVENT RATES ACCORDING TO BASELINE NT-proBNP LEVEL. The composite of cardiovascular death or HF hospitalization occurred at a rate of 1.9 (95% CI: 1.5-2.4) per 100 person-years in patients with an NT-proBNP <125 pg/mL compared with 8.7 (95% CI: 8.1-9.3) per 100 person-years in those with an NT-proBNP ≥125 pg/mL (Table 3). The relative risk in patients with NT-proBNP <125 pg/mL was lower for

all outcomes examined compared to those with an NT-proBNP ≥125 pg/mL (Central Illustration, Table 3, Figure 2). For example, after adjustment for other prognostic variables, the HR for the composite of cardiovascular death or HF hospitalization in patients with an NT-proBNP <125 pg/mL was 0.35 (95% CI: 0.27-0.46) compared with those with an NT-proBNP ≥125 pg/mL. In patients with LVEF ≥50%, event rates for all prognostic variables became smaller, but a similar trend according to NT-proBNP categories was observed (Supplemental Table 5).

COMPARISON OF CHARACTERISTICS, ECHOCARDIOGRAPHY FINDINGS, AND EVENT RATES IN I-PRESERVE WITH OTHER TRIALS WITH AN NT-proBNP ENTRY REQUIREMENT. Characteristics of patients with an NT-proBNP >300 pg/mL if not AF or >600 pg/mL if AF in I-PRESERVE and those in PARAGON-HF and DELIVER were shown in Supplemental Table 6. Patients in I-PRESERVE, compared with those in PARAGON-HF and DELIVER, were more often women, and had a lower body mass index, substantially worse NYHA functional class, lower prevalence of AF and diabetes, and better eGFR. Patients meeting the previously

mentioned NT-proBNP cutoff in I-PRESERVE had lower lateral E/e', larger left atrial area, and higher LVEF than in PARAGON-HF (Supplemental Table 7). Rates of the outcomes of interest in the control-arm group of each trial examined are shown in Figure 3. In I-PRESERVE, the rate of the primary composite of cardiovascular death or HF hospitalization was lower in patients with NT-proBNP <125 pg/mL (2.1; 95% CI: 1.5-2.9 per 100 person-years), compared with those with NT-proBNP ≥125 pg/mL (8.8; 95% CI: 8.0-9.7 per 100 person-years). The rate of the primary outcome in I-PRESERVE patients with an NT-proBNP >300 pg/mL if not AF (or >600 pg/mL if AF) was 11.0, 95% CI: 9.8-12.2 per 100 person-years, higher than the rates in PARAGON-HF (8.9; 95% CI: 8.2-9.7 per 100 person-years) and DELIVER patients with LVEF ≥45% (8.6; 95% CI: 7.9-9.5 per 100 person-years). Similar trends were observed for cardiovascular death, HF hospitalization, and all-cause death.

DISCUSSION

Among patients enrolled in I-PRESERVE based on a clinical diagnosis of HF, almost one-quarter had an NT-proBNP <125 pg/mL. The clinical characteristics and outcomes of these individuals differed markedly from participants with a higher NT-proBNP. Some of these differences were expected from prior studies, eg, patients with a lower NT-proBNP were younger, more often women, and more likely to have obesity.^{6-8,26-28} However, there were other notable differences, some of which might have been anticipated (eg, lower frequency of AF and chronic kidney disease) and some which were less predictable (eg, lower prevalence of coronary heart disease and diabetes). Conversely, some differences that may have been expected were not seen. Specifically, it is sometimes suggested that patients with a lower NT-proBNP might have another cause for their symptoms but the typical alternative diagnoses proposed, such as chronic obstructive pulmonary disease and anemia, were not more prevalent among patients with an NT-proBNP level <125 pg/mL (indeed both were less common in patients with a lower compared with higher NT-proBNP).²⁹⁻³² Patients with an NT-proBNP <125 pg/mL were less likely to have been hospitalized recently, had fewer signs of congestion, and had fewer electrocardiographic and echocardiographic abnormalities, but had similarly impaired health status evaluated by MLHFQ.

It is notable that the approximately one-quarter of patients with an NT-proBNP level <125 pg/mL identified in I-PRESERVE were, by protocol, excluded from contemporary HFmrEF/HFpEF trials such as DELIVER

TABLE 3 Outcomes According to NT-proBNP Categories

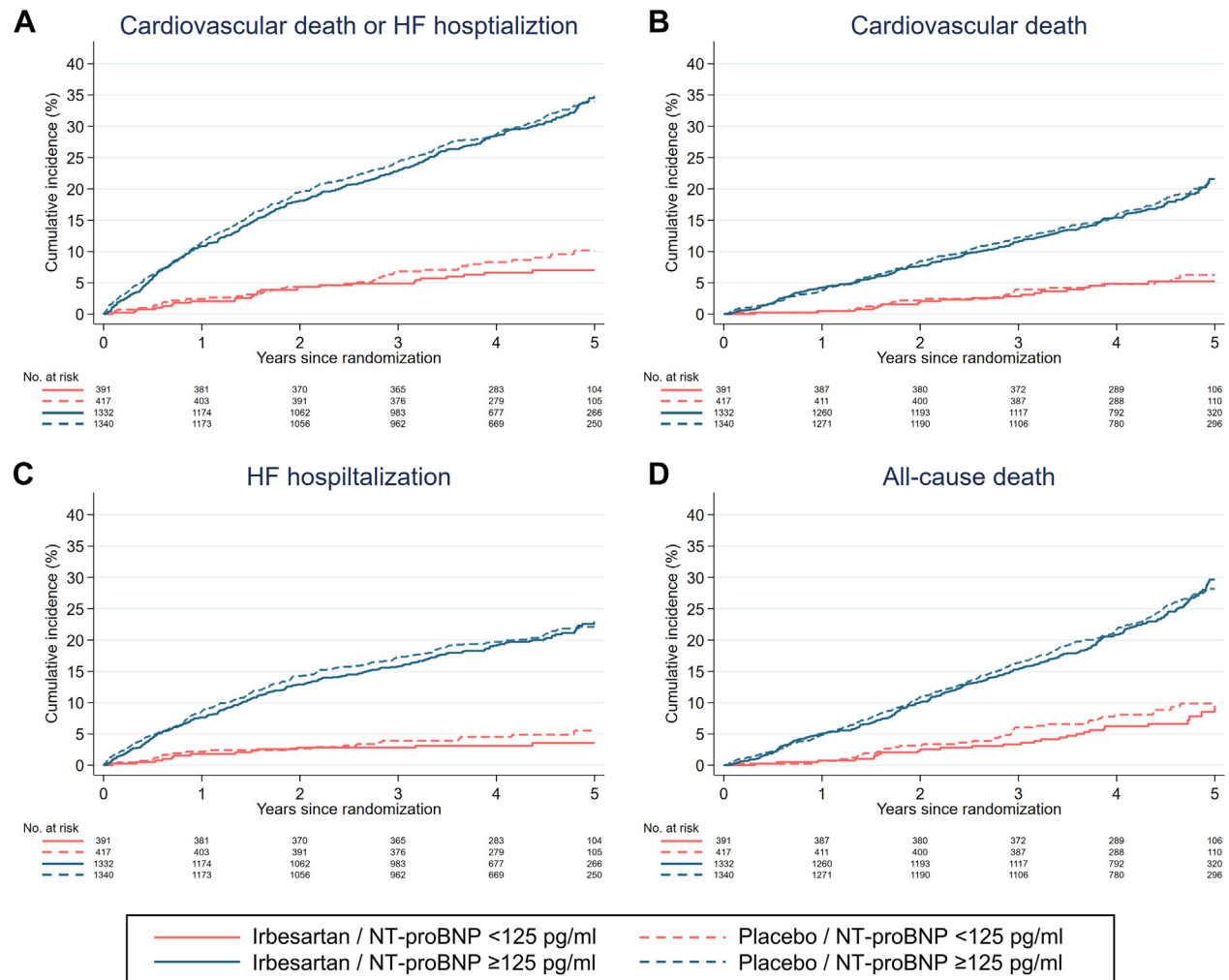
	Overall (N = 3,480)	NT-proBNP <125 pg/mL (n = 808)	NT-proBNP ≥125 pg/mL (n = 2,672)
Cardiovascular death or HF hospitalization	887 (25.5)	64 (7.9)	823 (30.8)
Event rate per 100 person-years (95% CI)	6.9 (6.4-7.3)	1.9 (1.5-2.4)	8.7 (8.1-9.3)
Model 1: HR (95% CI) ^a	—	0.22 (0.17-0.28) ^c	Reference
Model 2: HR (95% CI) ^b	—	0.35 (0.27-0.46) ^c	Reference
Cardiovascular death	515 (14.8)	42 (5.2)	473 (17.7)
Event rate per 100 person-years (95% CI)	3.7 (3.4-4.0)	1.2 (0.9-1.6)	4.5 (4.1-4.9)
Model 1: HR (95% CI) ^a	—	0.26 (0.19-0.36) ^c	Ref.
Model 2: HR (95% CI) ^b	—	0.43 (0.31-0.60) ^c	Ref.
HF hospitalization	552 (15.9)	33 (4.1)	519 (19.4)
Event rate per 100 person-years (95% CI)	4.3 (3.9-4.6)	1.0 (0.7-1.4)	5.5 (5.0-6.0)
Model 1: HR (95% CI) ^a	—	0.18 (0.13-0.26) ^c	Ref.
Model 2: HR (95% CI) ^b	—	0.32 (0.22-0.46) ^c	Ref.
All-cause death	735 (21.1)	65 (8.0)	670 (25.1)
Event rate per 100 person-years (95% CI)	5.2 (4.9-5.6)	1.9 (1.5-2.4)	6.3 (5.9-6.8)
Model 1: HR (95% CI) ^a	—	0.29 (0.22-0.37) ^c	Ref.
Model 2: HR (95% CI) ^b	—	0.48 (0.36-0.62) ^c	Ref.

^aModels were adjusted for treatment assignment. ^bModels were adjusted for treatment assignment, age, sex, region, systolic blood pressure, heart rate, body mass index, NYHA functional class, hospitalization for HF within previous 6 months, left ventricular ejection fraction, history of myocardial infarction, history of hypertension, history of diabetes, atrial fibrillation or atrial flutter in electrocardiography, and estimated glomerular filtration rate. ^cAll P values were <0.001.

Ref. = Reference; other abbreviations as in Table 1.

(NT-proBNP ≥300 pg/mL among patients not in AF/AFL and ≥600 pg/mL in patients with AF/AFL), and PARAGON-HF (>300 and >900 pg/mL, respectively unless hospitalized for HF within 9 months, in which case >200 and >600 pg/mL, respectively).

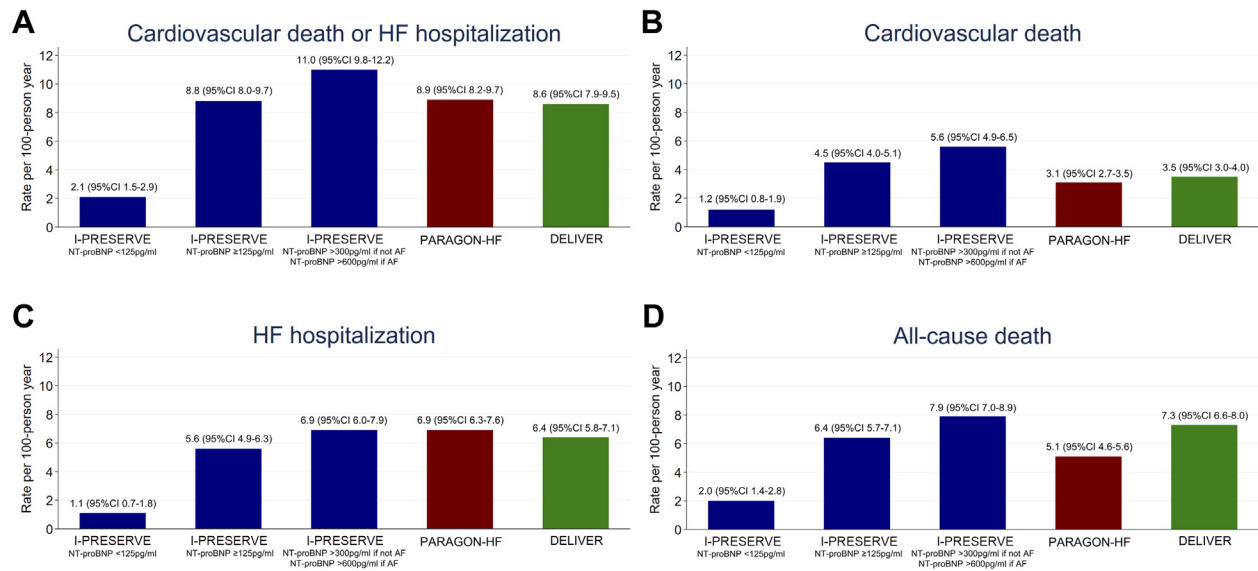
Not much is known about these excluded patients. The best existing information comes from 2 seminal observational cohort studies, which showed that some patients with a definitive diagnosis of HFpEF, defined by the gold standard of elevated resting or exercise-induced pulmonary capillary wedge pressure (PCWP), had low natriuretic peptide levels. However, these were carried out in single specialized centers (in a single country).^{6,7} The first was a report of 159 consecutive patients enrolled in the Northwestern University (Chicago) HFpEF Program with the clinical syndrome of HFpEF and an elevated resting PCWP. Of these, 46 (29%) had B-type natriuretic peptide ≤100 pg/mL. In a second much larger study of 581 consecutive participants undergoing invasive cardiopulmonary exercise testing for unexplained dyspnea at the Mayo Clinic between February 2006 and March 2018, 3 groups were described: patients with HFpEF and NT-proBNP ≥125 pg/mL (n = 263, 45%), patients with HFpEF and NT-proBNP <125 pg/mL (n = 157, 27%) and control subjects with normal hemodynamics, ie, PCWP <15 mm Hg at rest and <25 mm Hg on exercise

FIGURE 2 Kaplan-Meier Curves According to Baseline NT-proBNP Level

Kaplan-Meier curves among patients assigned to irbesartan or placebo according to baseline NT-proBNP level are plotted for (A) cardiovascular death or heart failure (HF) hospitalization, (B) cardiovascular death, (C) HF hospitalization, and (D) all-cause death. Patients with a lower NT-proBNP level (<125 pg/mL) had lower risks for all outcomes than those with a higher NT-proBNP level. Abbreviation as in [Figure 1](#).

(n = 161, 28%). Although these 2 studies were single-center studies in the United States, the prevalence of HFpEF with a low natriuretic peptide level was generally similar between these and our study, with a large number of cases from multiple countries. Thus, all 3 studies are complementary and have the same core findings: patients with low natriuretic peptide levels were younger, had better kidney function, were less likely to have coronary artery disease, were much less likely to have AF, and were much more likely to be obese. The proportion of patients with obesity was, however, much greater overall in the 2 U.S. studies than in I-Preserve.

All 3 studies showed that patients with lower natriuretic peptide levels have less right ventricular enlargement and, especially, less left atrial enlargement (although left atrial volumes were somewhat greater in I-PRESERVE than in the other 2 studies). More recently, the Mayo Clinic investigators have used 2-dimensional speckle tracking to show that left ventricular global longitudinal strain, right ventricular free wall strain and left atrial reservoir strain were higher (ie, less abnormal) in HFpEF patients with lower compared with higher natriuretic peptide levels (although left atrial reservoir strain was lower in both groups than in healthy control subjects).³³

FIGURE 3 Event Rates in I-PRESERVE Compared With Other Trials

The event rates for (A) cardiovascular death or HF hospitalization, (B) cardiovascular death, (C) HF hospitalization, and (D) all-cause death are shown according to the control arm of each trial; the placebo group in I-PRESERVE (NT-proBNP <125 pg/mL, NT-proBNP ≥125 pg/mL, and NT-proBNP >300 pg/mL if not atrial fibrillation (AF) or >600 pg/mL if AF), the valsartan group in PARAGON-HF, and the placebo group in DELIVER patients with left ventricular ejection fraction ≥45%. DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction; PARAGON-HF = Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction; other abbreviations as in [Figure 2](#).

There were several additional findings reported in I-PRESERVE not included in the prior studies, eg, pulse pressure, the prevalence of anemia, and the use of MRA therapy (although Verbrugge et al⁶ from the Mayo Clinic provided unique data on hemodynamics at rest and during exercise). One of the most interesting additional findings in I-PRESERVE was patients' self-reported health status (as assessed using the MLHFQ, scored 0-105, with a higher score indicating worse health status). The mean score of approximately 43, which was similar in the 2 groups defined by NT-proBNP level, was indicative of very significant impairment and worse than in several prior studies in both HFpEF and HFrEF.³⁴⁻⁴¹ Also, I-PRESERVE provided adjudicated event rates during long-term follow-up. Not surprisingly, patients with a low NT-proBNP had very low absolute event rates with only around 5% of patients experiencing HF hospitalization over 5 years and a slightly smaller proportion experiencing cardiovascular death; the corresponding proportions in participants with an NT-proBNP ≥125 pg/mL were close to 20% for both outcomes. However, Verbrugge et al⁶ have shown that, compared with control subjects, the event rates in patients with an NT-proBNP level <125 pg/mL are

still higher than in non-HF control subjects. Nevertheless, the low absolute event rates in patients with an NT-proBNP level <125 pg/mL present a major challenge for future morbidity/mortality trials wishing to include these patients, ie, much large sample sizes would be needed. Alternatively, the similarly depressed health status in patients with a low NT-proBNP may suggest that trials assessing the effect of therapy on symptoms and quality of life may be more feasible.

Skeptics may question whether participants in I-PRESERVE with an NT-proBNP level <125 pg/mL really had HF. Apart from the markedly reduced health status just described in the previous text, most patients had left atrial enlargement on echocardiography (as reported by investigators and supported by findings on echocardiography), about one-third had a verified hospitalization for HF in the 6 months before enrollment, many had radiologic pulmonary congestion or evidence of congestion on clinical examination, and three-quarters were treated with a diuretic. Consistent with the view that these patients do have cardiac dysfunction, the Mayo Clinic investigators recently showed that, as in HFpEF patients with higher natriuretic peptides, those with lower

natriuretic peptides demonstrated deterioration in left ventricular global longitudinal strain, right ventricular free wall strain, and left atrial reservoir strain over a median follow-up of 3.1 years, a progression that was not observed in healthy control subjects.³³ These investigators concluded that patients with lower natriuretic peptides represent individuals with an earlier stage of HFpEF than those with higher natriuretic peptide levels, but do experience progression of biventricular and atrial dysfunction over time. We could not examine this in our cohort because we did not have longitudinal echocardiographic or natriuretic peptide measurements.

Previously, when the effect of randomized treatment was examined in I-PRESERVE according to the NT-proBNP level divided at the median (339 pg/mL), irbesartan appeared to be beneficial in patients with a lower NT-proBNP level.⁴² Because the NT-proBNP <125 pg/mL group (examined in the present study) had many fewer events than in the <339 pg/mL group (described in the prior publication), only a trend to better outcomes was apparent in the present study in the irbesartan group. However, this retrospective finding, suggesting an unexpected differential effect of treatment, needs to be treated with great caution, especially as the overall trial was neutral. Nevertheless, the analyses of outcomes in the 2 NT-proBNP groups examined in the present study were adjusted for randomized treatment allocation.

STUDY LIMITATIONS. First, patients enrolled in clinical trials are selected according to specific inclusion and exclusion criteria, including requirements other than NT-proBNP and body mass index. Therefore, patients in I-PRESERVE do not reflect the full range of unselected “real world” patients with HFpEF, eg, individuals with a creatinine >2.5 mg/dL. Patients with LVEF in the range of 40% to 44%, included in the current definition of HFmrEF, were not enrolled in I-PRESERVE. Black patients, who are known to have lower levels of natriuretic peptides, were not well represented in I-PRESERVE. In I-PRESERVE, echocardiographic parameters were obtained only for patients in sinus rhythm, which may have resulted in an underestimation of the enlargement of the left atrial area and indices of diastolic dysfunction indexes. We were unable to investigate the detailed biological differences between patients with lower and higher NT-proBNP levels and a recent proteomic investigation has suggested that high NT-proBNP levels in patients with HFpEF are a marker of fibrosis and inflammation.^{43,44} More detailed characterization of potential differences between patients with lower and higher NT-proBNP levels is therefore of interest in future studies, eg, in identifying alternative

diagnostic markers and biomarkers improving risk prediction in HFpEF.

CONCLUSIONS

Almost one-quarter of patients in I-PRESERVE had a low NT-proBNP level, suggesting that there are many such patients in the “real world” HFmrEF/HFpEF population (and the need for rigorous diagnostic investigation). Although HFmrEF/HFpEF patients with a low NT-proBNP have relatively low rates of hospitalization and death, they have a marked reduction in health status as measured by their MLHFQ. These findings emphasize the important need for treatments that improve symptoms and quality of life in HFmrEF/HFpEF, even among patients with low NT-proBNP.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: One-quarter of patients with HFmrEF/HFpEF had low NT-proBNP levels, and these patients had lower risks of cardiovascular death and HF hospitalization but had similarly impaired health status compared with those with a higher NT-pro BNP.

TRANSLATIONAL OUTLOOK: Treatments that improve symptoms and quality of life are needed even in HFmrEF/HFpEF patients with low NT-proBNP levels who, despite low rates of morbidity and mortality, have substantially impaired health status.

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- KEY WORDS** body mass index, heart failure, heart failure with preserved ejection fraction, natriuretic peptide
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- APPENDIX** For supplemental figures and tables, please see the online version of this paper.