

# N-terminal pro-B-type natriuretic peptide concentrations, testing and associations with worsening heart failure events

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## Abstract

**Aims** In patients with heart failure (HF), we aimed to assess (i) the time trends in N-terminal pro-B-type natriuretic peptide (NT-proBNP) testing; (ii) patient characteristics associated with NT-proBNP testing; (iii) distribution of NT-proBNP levels, focusing on the subgroups with (WHFE) vs. without (NWHFE) a worsening HF event, defined as an HF hospitalization; and (iv) changes of NT-proBNP levels over time.

**Methods and results** NT-proBNP testing and levels were investigated in HF patients enrolled in the Swedish Heart Failure Registry (SwedeHF) linked with the Stockholm Creatinine Measurements project from January 2011 to December 2018. Index date was the first registration in SwedeHF. Patterns of change in NT-proBNP levels before (in the previous  $6 \pm 3$  months) and after (in the following  $6 \pm 3$  months) the index date were categorized as follows: (i)  $<3000$  ng/L at both measurements = stable low; (ii)  $<3000$  ng/L at the first measurement and  $\geq 3000$  ng/L at the second measurement = increased; (iii)  $\geq 3000$  ng/L at the first measurement and  $<3000$  ng/L at the second measurement = decreased; and (iv)  $\geq 3000$  ng/L at both measurements = stable high. Univariable and multivariable logistic regression models, expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs), were performed to assess the associations between (i) clinical characteristics and NT-proBNP testing and (ii) changes in NT-proBNP from 6 months prior to the index date and the index date and a WHFE. Consistency analyses were performed in HF with reduced ejection fraction (HFrEF) alone. A total of 4424 HF patients were included (median age 74 years, women 34%, HFrEF 53%), 33% with a WHFE. NT-proBNP testing increased over time, up to 55% in 2018, and was almost two-fold as frequent, and time to testing was less than half, in patients with WHFE vs. NWHFE. Independent predictors of testing were WHFE, higher heart rate, diuretic use, and preserved ejection fraction. Median NT-proBNP was 3070 ng/L (Q1–Q3: 1220–7395), approximately three-fold higher in WHFE vs. NWHFE. Compared with stable low NT-proBNP levels, increased (OR 4.27, 95% CI 2.47–7.37) and stable high levels (OR 2.48, 95% CI 1.58–3.88) were independently associated with a higher risk of WHFE. Results were consistent in the HFrEF population.

**Conclusions** NT-proBNP testing increased over time but still was only performed in half of the patients. Testing was associated with a WHFE, with features of more severe HF and for differential diagnosis purposes. Increased and stable high levels were associated with a WHFE. Overall, our data highlight the potential benefits of carrying further implementation of NT-proBNP testing in clinical practice.

**Keywords** Heart failure; NT-proBNP; HFrEF; HFpEF; Outcomes; SwedeHF; SCREAM

Received: 9 June 2023; Revised: 23 October 2023; Accepted: 16 November 2023

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## Introduction

Heart failure (HF) is the leading cause of hospitalization in the Western world and is associated with poor survival and quality of life.<sup>1</sup> Worsening HF events (WHFEs), that is, the development of progressively escalating symptoms and signs of HF requiring intravenous diuretic treatment or hospitalization, represent a substantial burden for healthcare systems and are associated with markedly worse prognosis.<sup>2,3</sup> Approximately one out of six patients with HF with reduced ejection fraction (HFrEF) reports a WHFE within 18 months from the diagnosis, which is associated with a 2 year mortality rate of approximately 22% and a 30 day readmission rate of 56%.<sup>2</sup>

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are released by ventricular cardiomyocytes in response to an increased wall stress and neurohormonal stimulation. The measurement of NT-proBNP is recommended by international HF guidelines for diagnosis, classification, assessing disease severity, and prognostic stratification.<sup>4,5</sup> Limited implementation of guideline recommendations in clinical practice has been extensively documented, in particular regarding treatment.<sup>6,7</sup> Moreover, NT-proBNP is used as an eligibility criterion in HF trials and enriches for cardiovascular vs. non-cardiovascular events.<sup>8</sup> However, data on the implementation of NT-proBNP testing in clinical practice are overall sparse. Although increases in the concentration of NT-proBNP over time have been associated with higher risk of subsequent mortality/morbidity, there is limited real-world evidence on the use of and distribution of NT-proBNP levels in patients with HF, especially in those following a WHFE.<sup>9</sup>

The aim of the present study was to assess in a real-world HF population (i) the prevalence of and the patient characteristics associated with the likelihood of NT-proBNP testing in patients with HF with vs. without a worsening HF event (WHFE vs. NWHFE); (ii) the distribution and patterns of changes in NT-proBNP levels in patients with vs. without a WHFE; and (iii) their associations with WHFEs.

## Methods

### Data sources

The Swedish Heart Failure Registry (SwedeHF) is a nationwide health quality and research registry in Sweden with continuous enrolment (<https://www.ucl.ac.uk/rikssvikt-en/>). Until April 2017, the only inclusion criterion was clinician-judged HF, and thereafter, a diagnosis of HF according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, and I13.2. The

coverage of prevalent HF in Region Stockholm was approximately 29% in 2021. For the current analysis, SwedeHF was linked to the Stockholm Creatinine Measurements (SCREAM) project by the unique personal identification number, which all the residents in Sweden are assigned.

The SCREAM project is a repository of laboratory data performed in connection with a healthcare encounter from individuals residing in the region of Stockholm.<sup>10</sup> The criterion to have laboratory data extracted (including NT-proBNP) is to undergo at least one plasma creatinine or urine albumin test during 2006–18, which occurred in ~98% of all patients with a diagnosis of cardiovascular disease during that time.<sup>10</sup> SCREAM provided all the lab measurements for the current study, which thus includes only the patients registered in the SwedeHF that resided in Region Stockholm.

Additional data on comorbidities and HF hospitalizations were obtained by linkage to The Regional Healthcare Utilization Database (VAL), which contains information on all consultations in primary and specialist outpatient care, as well as hospitalizations in Region Stockholm, reported as clinical diagnoses (ICD-10 codes) and procedures. Socioeconomic data were obtained from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA).

This analysis and the linkage across the different data sources were approved by the Swedish Ethical Review Authority (DNR 2017-79331, 2019-02199, and 2020-06719).

### Selection criteria and definitions

Adult patients were included in the present study if registered in both SwedeHF and SCREAM and with registration in SwedeHF between 15 January 2011 and 17 December 2018. If a patient had >1 registration in SwedeHF, the first one was considered, and the date of this registration was the index date. Exclusion criteria were (i) new-onset HF, defined by (a) the reporting of any ICD-10 for HF (I110, I130, I132, I255, I420, I423, I425, I426, I427, I428, I429, I43, I50, J81, K761, and R57) in the 6 months prior to the first registration in SwedeHF and/or (b) an HF duration of <6 months in SwedeHF; (ii) missing entry for ejection fraction (EF) in SwedeHF; (iii) registrations with reused or changed personal identification numbers; (iv) patients who moved from Stockholm prior to the index date; (v) patients without match within the 14 days in VAL-SwedeHF; and (vi) patients with index date after date of death (registration error).

HFrEF was defined as EF < 40%. A WHFE occurred whether a patient had a registration as inpatient at the index date and HF was verified as being the cause for hospitalization in VAL. All the remaining patients were classified as NWHFE and their index date was the outpatient registration in SwedeHF. Baseline NT-proBNP was the lab value recorded at index date or in

the previous 14 days. Six months of NT-proBNP assessment before and after the index date was defined as  $6 \pm 3$  months before or after index.

## Analyses and statistical methods

To assess trends in NT-proBNP testing over time, we calculated the proportion of patients with at least one NT-proBNP measurement per every calendar year (nominator) with respects to all patients included and alive/at risk till 31 December of the previous year (denominator). Cumulative incidence curves for time from index date to first test were fitted. Number of NT-proBNP tests per patient within the first 6 months, first and second year after the index date, was also reported. Patient characteristics in tested vs. non-tested patients were presented as number (percentage) and compared with the  $\chi^2$  test for categorical variables, whereas continuous variables were reported as median [first (Q1) to third (Q3) quartile] and compared by the Kruskal–Wallis test. The association between patient characteristics and the likelihood being tested was assessed by univariable logistic regression models. All the variables associated with NT-proBNP testing with a *P*-value  $< 0.10$  in the crude models were then included in a multivariable model.

NT-proBNP concentrations and distributions at the index date were presented as median, Q1–Q3, minimum–maximum, and number (percentage) per 1000-unit increase, respectively.

The association between changes in NT-proBNP from 6 months prior to the index date and the index date and the occurrence of a WHFE was analysed by univariable and multivariable logistic regression models (adjusted for the patient characteristics reported in *Table 1*). Results were reported as odds ratios (ORs) with 95% confidence intervals (95% CIs).

Patterns of change in NT-proBNP levels before (in the previous  $6 \pm 3$  months) and after (in the following  $6 \pm 3$  months) the index date were categorized by using a cut-off of 3000 ng/L, given the distribution in our population: (i)  $< 3000$  ng/L at both measurements = stable low group; (ii)  $< 3000$  ng/L at the first measurement and  $\geq 3000$  ng/L at the second measurement = increased group; (iii)  $\geq 3000$  ng/L at the first measurement and  $< 3000$  ng/L at the second measurement = decreased group; and (iv)  $\geq 3000$  ng/L at both measurements = stable high group.

In our multivariable models, missing data for study covariates were handled by multiple imputation ( $n = 20$ ; covariates included in the models are marked in *Table 1*) using the Multivariate Imputation by Chained Equations package in R.

All the analyses were run in the overall population, and in the baseline, WHFE vs. NWHFE populations separately. A consistency analysis only in HFREF patients was performed.

Statistical analyses were performed using R Version 4.0.2 (R Core Team 2019). The level of significance was set to 5%, two-sided.

## Results

### N-terminal pro-B-type natriuretic peptide testing

Of 4426 HF patients included in the analyses (median age 74 years [66, 82]; women 34%, HFREF 53%), 33% had a WHFE, and of these, 70% were tested for NT-proBNP at least once during the study period, whereas in patients with NWHFE, testing was only 35%.

*Figure 1A* shows the proportions of HF patients tested for NT-proBNP per calendar year, showing overall increasing trends over time, with 54% of HF patients with WHFE and 53% of those with NWHFE tested for NT-proBNP in 2018. Median number of days from the index date to first NT-proBNP testing was 180, shorter in patients with WHFE vs. NWHFE (100 vs. 231 days; *Figure 1B*). The mean number of NT-proBNP tests within 1 year from the index date was approximately two-fold higher in patients with WHFE vs. NWHFE ( $2.8 \pm 4.8$  vs.  $1.6 \pm 2.5$ ; Supporting Information, *Figure S1* and *Table S1*), whereas the median number was 1 regardless of having reported or not a WHFE. Number of NT-proBNP tests within 1 year after the index date was higher in younger patients (age  $< 75$  years), those with reduced kidney function, and inpatients, without major differences across genders and patients with/without atrial fibrillation (Supporting Information, *Figure S1* and *Tables S1* and *S2*). Testing was more likely performed within 14 days prior to the index date, in 71% of WHFE and 35% of NWHFE (Supporting Information, *Figure S2*). Results were consistent in the 2343 patients with HFREF as compared with the overall HF cohort.

### Patient profiles according to N-terminal pro-B-type natriuretic peptide testing

Patient characteristics of those tested vs. not tested at index date are reported in *Table 1* for the overall population and in Supporting Information, *Table S3* for the HFREF subgroup. The HFREF population was slightly younger, with a higher prevalence of males and higher New York Heart Association (NYHA) class compared with the overall population, but otherwise quite similar.

Regardless of a WHFE, tested patients were more likely to receive diuretics. In those with a WHFE, tested patients were younger, more likely to have lower NYHA class and hypertension, and less likely to have a higher education. Of NWHFE patients, those who were tested were older and with HF with preserved ejection fraction (HFpEF), had higher NYHA

Table 1 Baseline characteristics of study participants stratified by the presence or absence of worsening heart failure event

Variables	WHFE			NWHFE			P-value tested vs. NWHFE)
	Missing (%)	Tested	Not tested	P-value	Tested	Not tested	
N (%)	4426	1021 (23.1)	428 (9.7)		1037 (23.4)	1940 (43.8)	
Sex: Male <sup>a</sup>	0.0	632 (61.9)	255 (59.6)	0.442	668 (64.4)	1360 (70.1)	<0.001
Age (years)	0.0	78.0 [69.0, 85.0]	80.0 [72.0, 86.0]	0.025	74.0 [65.0, 81.0]	72.0 [64.0, 79.0]	0.004
Age (years) ≥ 75 <sup>a</sup>	0.0	610 (59.7)	289 (67.5)	0.006	497 (47.9)	813 (41.9)	0.002
Index year 2015–18 <sup>a</sup>	0.0	234 (22.9)	52 (12.1)	<0.001	583 (56.2)	1066 (54.9)	0.531
Index year	0.0	2012.0	2012.0	0.132	2016.0	2015.0	<0.001
		[2011.0, 2014.0]	[2011.0, 2013.0]		[2012.0, 2017.0]	[2013.0, 2017.0]	
LVEF (%) <sup>a</sup>	0.0	550 (53.9)	246 (57.5)	0.453	463 (44.6)	1084 (55.9)	<0.001
HFREF		199 (19.5)	77 (18.0)		264 (25.5)	486 (25.1)	<0.001
HFmrEF		272 (26.6)	105 (24.5)		310 (29.9)	370 (19.1)	<0.001
HFpEF							<0.001
NYHA class	28.5			0.027			<0.001
I		41 (6.4)	12 (4.3)		96 (14.0)	177 (11.4)	
II		268 (41.7)	94 (33.3)		298 (43.6)	769 (49.4)	
III		282 (43.9)	151 (53.5)		269 (39.3)	587 (37.7)	
IV		51 (7.9)	25 (8.9)		21 (3.1)	24 (1.5)	
NYHA class III–IV <sup>a</sup>	28.5	333 (51.9)	176 (62.4)	0.004	290 (42.4)	611 (39.2)	<0.001
Mean arterial pressure	2.3	87.5 [80.0, 96.4]	88.3 [80.0, 96.7]	0.837	89.5 [81.0, 96.7]	88.3 [80.0, 96.7]	0.347
Mean arterial pressure > 90 <sup>a</sup>	2.3	398 (39.3)	169 (40.7)	0.668	445 (43.8)	825 (43.9)	0.997
Systolic blood pressure (mmHg)	2.3	120.0 [110.0, 135.0]	120.0 [110.0, 133.5]	0.976	121.0 [110.0, 139.0]	120.0 [110.0, 135.0]	0.025
Diastolic blood pressure (mmHg)	2.3	70.0 [60.0, 80.0]	70.0 [60.0, 80.0]	0.735	70.0 [64.0, 80.0]	70.0 [65.0, 80.0]	0.658
Heart rate (b.p.m.)	4.8	73.0 [65.0, 85.0]	73.0 [65.0, 82.8]	0.832	71.0 [63.0, 80.0]	70.0 [62.0, 78.0]	<0.001
Heart rate (b.p.m.) > 70 <sup>a</sup>	4.8	546 (55.0)	229 (55.9)	0.811	502 (51.4)	792 (43.2)	<0.001
BMI (kg/m <sup>2</sup> )	40.1	25.6 [22.3, 29.8]	25.7 [22.5, 29.9]	0.579	26.5 [23.4, 30.5]	26.6 [23.5, 29.9]	0.600
BMI (kg/m <sup>2</sup> ) ≥ 30	40.1	178 (24.1)	59 (24.5)	0.970	137 (27.3)	287 (24.6)	0.267
Haemoglobin (mg/L)	38.8	125.0 [113.0, 139.0]	122.0 [109.0, 137.2]	0.016	132.0 [121.0, 143.0]	130.0 [117.5, 141.0]	0.010
Anaemia	38.8	501 (49.7)	186 (54.7)	0.125	277 (33.9)	222 (40.7)	0.012
Sodium (mEq/L)	20.4	140.0 [138.0, 143.0]	140.0 [138.0, 142.0]	0.048	140.0 [138.0, 142.0]	140.0 [138.0, 142.0]	0.113
Sodium (mEq/L) > 135	20.4	928 (90.9)	303 (86.8)	0.038	942 (92.6)	1067 (94.1)	0.200
Potassium	19.3	4.0 [3.7, 4.3]	4.0 [3.7, 4.4]	0.129	4.2 [3.9, 4.5]	4.2 [4.0, 4.5]	0.016
Dyskalaemia	19.3			0.272			0.589
Normokalaemia		922 (90.5)	322 (90.7)		947 (92.4)	1072 (91.5)	<0.001
Hypokalaemia		78 (7.7)	22 (6.2)		39 (3.8)	45 (3.8)	<0.001
Hyperkalaemia		19 (1.9)	11 (3.1)		39 (3.8)	55 (4.7)	0.179
eGFR	18.9	54.8 [39.5, 74.3]	51.3 [37.2, 73.9]	0.220	65.2 [47.1, 83.5]	68.2 [50.3, 87.0]	<0.001
eGFR categorized <sup>a</sup>	18.9			0.263			0.086
≤30		140 (13.7)	47 (13.1)		75 (7.3)	68 (5.7)	
>30 to <60		449 (44.0)	176 (48.9)		362 (35.3)	386 (32.6)	
≥60		432 (42.3)	137 (38.1)		589 (57.4)	730 (61.7)	
Smoking <sup>a</sup>	36.5	97 (14.5)	32 (11.5)	0.259	65 (12.2)	163 (12.2)	<0.001
Diabetes <sup>a</sup>	0.0	402 (39.4)	160 (37.4)	0.516	296 (28.5)	544 (28.0)	<0.001
Atrial fibrillation/flutter <sup>a</sup>	0.0	729 (71.4)	318 (74.3)	0.289	729 (71.4)	1126 (58.0)	0.057
Ischaemic heart disease <sup>a</sup>	0.0	579 (56.7)	248 (57.9)	0.708	518 (50.0)	1014 (52.3)	0.244
Hypertension <sup>a</sup>	0.0	837 (82.0)	331 (77.3)	0.049	747 (72.0)	1353 (69.7)	0.206

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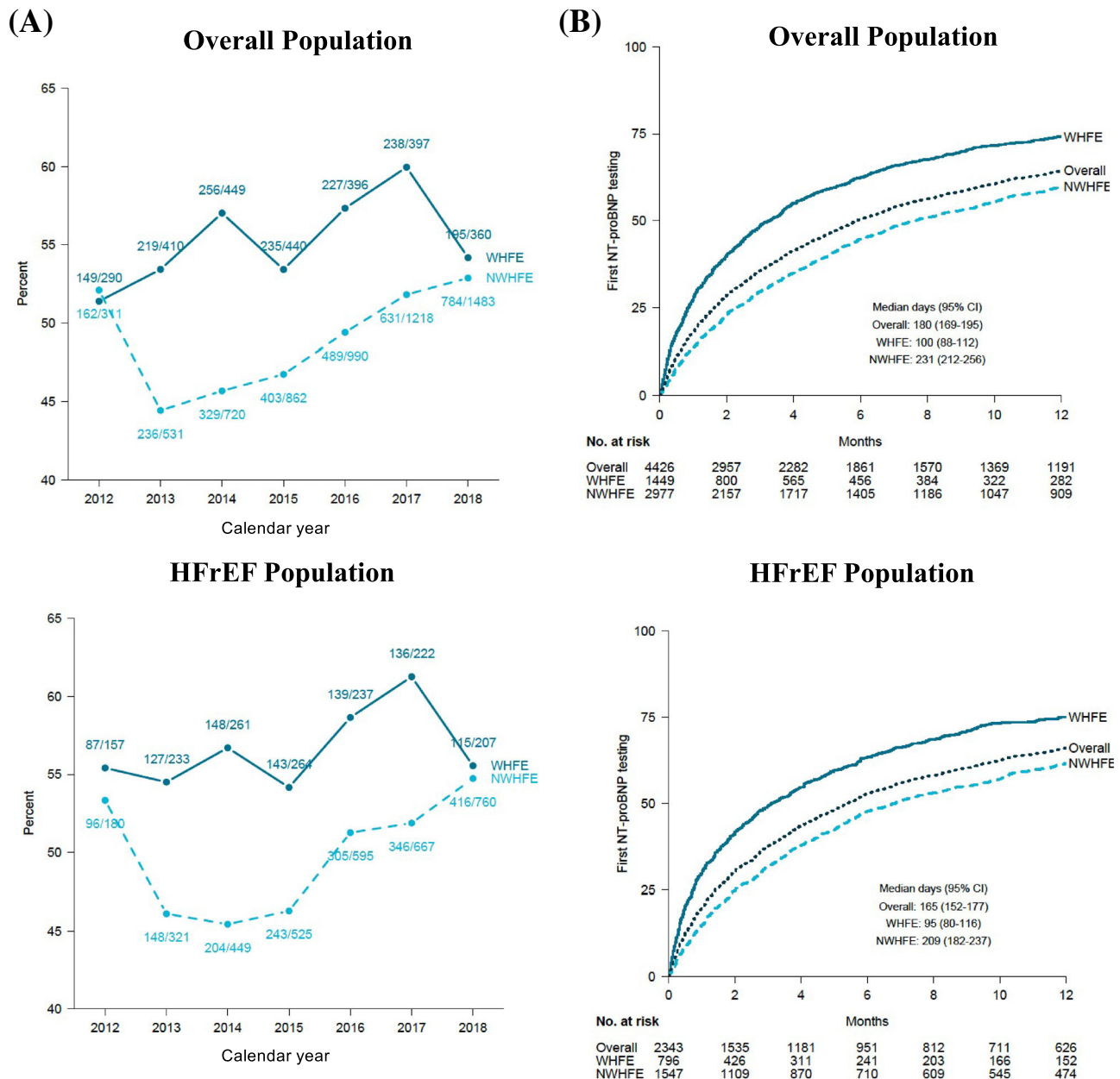
Table 1 (continued)

Variables	WHFE			NWHFE			P-value tested (WHFE vs. NWHFE)
	Missing (%)	Tested	Not tested	P-value	Tested	Not tested	
Peripheral artery disease	0.0	176 (17.2)	72 (16.8)	0.908	118 (11.4)	234 (12.1)	0.624
Stroke/TIA <sup>a</sup>	0.0	199 (19.5)	94 (22.0)	0.319	147 (14.2)	265 (13.7)	0.739
Valvular disease <sup>a</sup>	0.0	382 (37.4)	197 (46.0)	0.003	281 (27.1)	506 (26.1)	0.579
Liver disease <sup>a</sup>	0.0	50 (4.9)	23 (5.4)	0.805	37 (3.6)	75 (3.9)	0.760
Malignant cancer <sup>a</sup>	0.0	164 (16.1)	61 (14.3)	0.430	166 (16.0)	300 (15.5)	0.737
Musculoskeletal/connective tissue diseases <sup>a</sup>	0.0	640 (62.7)	260 (60.7)	0.526	639 (61.6)	1162 (59.9)	0.381
Dementia	0.0	32 (3.1)	21 (4.9)	0.137	21 (2.0)	33 (1.7)	0.626
COPD <sup>a</sup>	0.0	231 (22.6)	95 (22.2)	0.913	212 (20.4)	313 (16.1)	0.004
Severe bleeding	0.0	0 (0.0)	0 (0.0)	NaN	0 (0.0)	0 (0.0)	NaN
Charlson comorbidity index	0.0	4.0 [2.0, 6.0]	4.0 [2.0, 7.0]	0.994	3.0 [2.0, 5.0]	3.0 [2.0, 5.0]	0.069
ACE-/ARB/ARNI <sup>a</sup>	1.5	793 (79.7)	322 (78.0)	0.511	850 (82.9)	1735 (90.1)	<0.001
Beta-blocker <sup>a</sup>	0.8	916 (90.6)	369 (88.7)	0.321	918 (89.2)	1769 (91.5)	0.052
MRA <sup>a</sup>	1.6	392 (39.4)	158 (38.6)	0.825	436 (42.6)	768 (39.8)	0.151
Diuretic <sup>a</sup>	1.3	936 (93.5)	355 (86.4)	<0.001	786 (76.8)	1300 (67.3)	<0.001
Device therapy CRT/ICD <sup>a</sup>	0.6	82 (8.1)	32 (7.5)	0.787	83 (8.0)	217 (11.2)	0.007
Digoxin <sup>a</sup>	0.9	150 (14.8)	57 (13.6)	0.624	123 (12.0)	223 (11.5)	0.744
Platelet inhibitor <sup>a</sup>	1.2	380 (38.0)	158 (37.7)	0.966	319 (31.1)	650 (33.7)	0.160
Oral anticoagulants <sup>a</sup>	0.9	517 (51.4)	214 (51.1)	0.959	549 (53.4)	1044 (54.0)	0.751
Statin <sup>a</sup>	0.8	486 (48.0)	178 (42.5)	0.064	476 (46.3)	998 (51.7)	0.005
Nitrate <sup>a</sup>	1.0	194 (19.2)	73 (17.5)	0.489	129 (12.6)	206 (10.7)	0.138
Follow-up referral HF nurse clinic <sup>a</sup>	7.0	403 (43.1)	150 (41.0)	0.537	591 (60.4)	1281 (69.8)	<0.001
Follow-up referral speciality primary care/other <sup>a</sup>	3.8	323 (33.4)	141 (36.3)	0.327	217 (21.5)	231 (12.2)	<0.001
Living alone <sup>a</sup>	0.0	569 (55.8)	247 (57.7)	0.538	504 (48.6)	876 (45.2)	0.081
Education university <sup>a</sup>	2.7	176 (17.9)	94 (22.8)	0.039	275 (27.2)	530 (27.9)	0.723
Disposable income (100 SEK) above medium <sup>a</sup>	0.0	458 (44.9)	196 (45.8)	0.800	533 (51.4)	1030 (53.1)	0.391

ACE-/ARB/ARNI, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor agonists; NWHFE, no worsening heart failure event; NYHA, New York Heart Association; TIA, transitory ischaemic attack; WHFE, worsening heart failure event.

<sup>a</sup>Variables considered for multiple imputation and Cox/logistic regression models.

**Figure 1** Trends in N-terminal pro-brain natriuretic peptide (NT-proBNP) testing overtime in the overall population and in heart failure with reduced ejection fraction (HFrEF) (panel A) and time from the index date to the first NT-proBNP testing in the overall population and in HFrEF (panel B). CI, confidence interval; NWHFE, no worsening heart failure event; WHFE, worsening heart failure event.

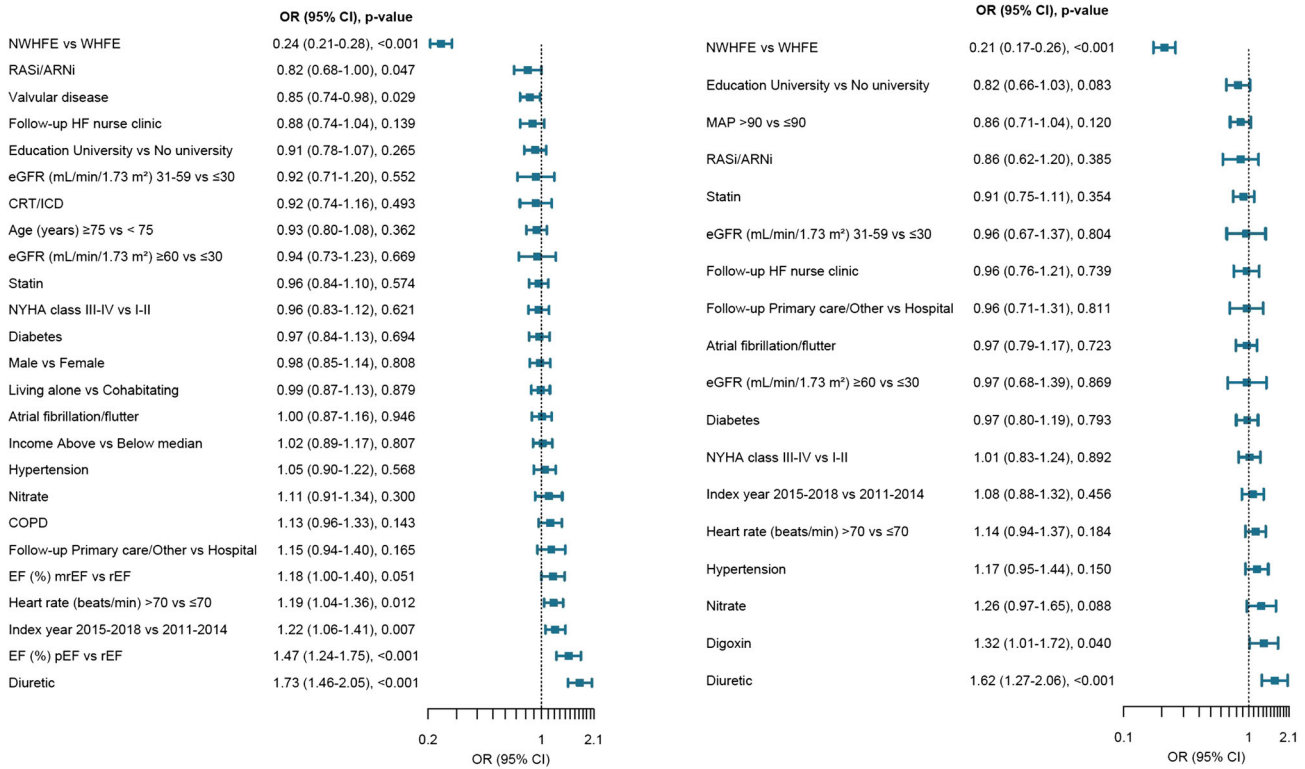


class and higher heart rate, and were less likely to have anaemia, more likely to have chronic obstructive pulmonary disease, less likely to receive renin-angiotensin-aldosterone inhibitors/angiotensin receptor neprilysin inhibitors (RASi/ARNi) or cardiac resynchronization therapy/implantable cardioverter defibrillator (ICD/CRT), and less likely followed up in HF nurse-led clinic and more likely in primary care. Results were overall consistent in the HFrEF subgroup.

### Independent predictors of N-terminal pro-B-type natriuretic peptide testing

Independent predictors of the likelihood to undergo NT-proBNP testing in the overall population were a WHFE, receiving diuretics, HFpEF vs. HFrEF, a more recent registration in SwedeHF, higher heart rate, no history of valvular disease, and no use of RASi/ARNi (Figure 2 and Supporting Informa-

**Figure 2** Forest plots showing the independent association between patient characteristics and N-terminal pro-B-type natriuretic peptide testing in the overall (left) and heart failure (HF) with reduced ejection fraction (rEF) (right) study population in the multivariable models. CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; mrEF, mildly reduced EF; NWHFE, no worsening heart failure event; NYHA, New York Heart Association; OR, odds ratio; pEF, preserved EF; RASi/ARNi, renin-angiotensin-aldosterone inhibitors/angiotensin receptor neprilysin inhibitors; WHFE, worsening heart failure event.

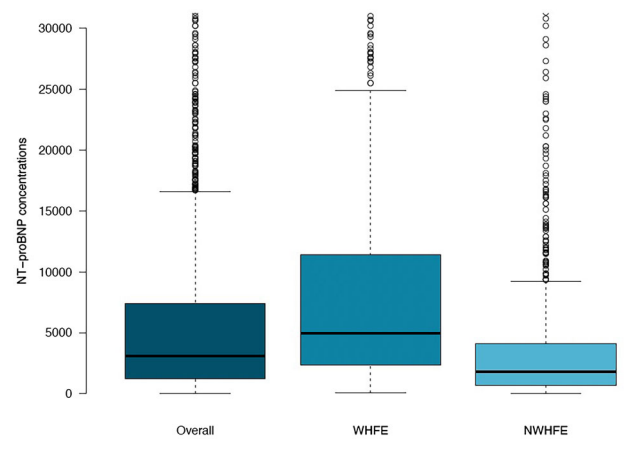


tion, *Table S4*). In HF rEF, having a WHFE and use of diuretics and digoxin were independently associated with the likelihood of testing (*Figure 2* and Supporting Information, *Table S5*).

### N-terminal pro-B-type natriuretic peptide levels at the index date

The distribution of NT-proBNP was skewed, with a median value of 3070 ng/L (1220, 7395) (*Figure 3*). The median value in patients with WHFE was approximately three-fold higher than with NWHFE (4950 ng/L [2350, 11 400] vs. 1800 ng/L [672, 4120], respectively). Whereas 33% of patients with NWHFE had NT-proBNP ≤ 1000 ng/L, in WHFE, it was only 8%. In WHFE vs. NWHFE (Supporting Information, *Table S6*), 35% vs. 12%, respectively, had NT-proBNP > 8000 ng/L, and 20% vs. 6%, respectively, had values > 14 000 ng/L.

**Figure 3** Box plots of N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations at index date. NWHFE, no worsening heart failure event; WHFE, worsening heart failure event.



In patients with HF<sub>rEF</sub>, NT-proBNP levels were higher compared with the overall cohort (median 4150 ng/L [1760, 10 900], 6795 ng/L [3005, 15 275] in WHFE and 2370 ng/L [1060, 4940] in NWHFE) (Supporting Information, *Table S7*).

### Patterns in N-terminal pro-B-type natriuretic peptide changes before and after the index date

A total of 859 patients had a measurement in the previous  $6 \pm 3$  months before the index, of which 423 had HF<sub>rEF</sub>. Compared with NT-proBNP levels before the index date, levels after the index date decreased by median  $-97$  ng/L [ $-1608$ ,  $1040$ ] in the overall cohort. Decreases were larger in the group with WHFE ( $-258$  ng/L [ $-2582$ ,  $1325$ ]) compared with NWHFE ( $-18$  ng/L [ $-806$ ,  $839$ ]); the corresponding NT-proBNP decreases in the HF<sub>rEF</sub> group were  $-199$  ng/L [ $-2330$ ,  $1004$ ],  $-625$  ng/L [ $-3703$ ,  $1211$ ], and  $-46$  ng/L [ $-1084$ ,  $957$ ].

*Table 2* reports categorical changes in NT-proBNP, that is, stable low, decreased, increased, and stable high, considering as time points 6 months prior to the index date, the index date, and 6 months after the index date. Results in relevant subgroups are reported in Supporting Information, *Tables S8–S11*. Prior to the index date, most patients (61%) had stable low NT-proBNP levels, 21% had stable high levels, 12% had increased, and only 6% had decreased levels. In the WHFE group, 31% of HF patients had stable high and 20% had increased levels (39% and 23% in HF<sub>rEF</sub>, respectively), whereas in those with an NWHFE, corresponding estimates were 12% and 6% (16% and 7% in HF<sub>rEF</sub>, respectively), and 75% (49% in HF<sub>rEF</sub>) had stable low levels. As compared with stable low NT-proBNP levels, increased (OR 4.27, 95%

CI 2.47–7.37) and stable high levels (OR 2.48, 95% CI 1.58–3.88) were independently associated with a higher risk of WHFE, whereas no significant association was found for decreasing levels (OR 1.05, 95% CI 0.52–2.09; Supporting Information, *Table S12*). Results were consistent in the HF<sub>rEF</sub> population (Supporting Information, *Table S12*).

Changes after the index date were assessed in 888 patients (466 with HF<sub>rEF</sub>). Six months after the index date, most patients had stable levels, either high (39%) or low (38%). In the WHFE group, 48% had stable high and 18% had decreased NT-proBNP levels (51% and 21% in HF<sub>rEF</sub>, respectively), whereas in those with an NWHFE, corresponding estimates were 30% and 10% (34% and 11% in HF<sub>rEF</sub>, respectively), and 51% (46% in HF<sub>rEF</sub>) maintained stable low NT-proBNP levels.

## Discussion

We evaluated testing rates, predictors, and values of NT-proBNP testing in adults with HF from the Stockholm region from 2011 to 2018 and observed increased testing rates over time, which may reflect improved awareness about HF and the better recognized role of NT-proBNP in risk stratification and monitoring disease progression. However, in 2018, only roughly 55% of patients were tested, which is suboptimal. As these patients are usually followed up for HF at least once per year, this implies that NT-proBNP testing was performed in less than half of these medical encounters. Seventy per cent of the tests performed in patients with WHFE was within 2 weeks before the index date, possibly indicating a laboratory assessment at the time of hospital admission;

**Table 2** Patterns of change in N-terminal pro-brain natriuretic peptide levels before (in the previous  $6 \pm 3$  months) and after (in the following  $6 \pm 3$  months) the index date in the overall population, according to the presence of a worsening heart failure event, and in the sub-population with heart failure with reduced ejection fraction

	Stable low	Decreased	Increased	Stable high
Before index date—Whole population				
Overall	527 (61.4%)	50 (5.8%)	104 (12.1%)	178 (20.7%)
WHFE	170 (44.2%)	18 (4.7%)	78 (20.3%)	119 (30.9%)
NWHFE	357 (75.3%)	32 (6.8%)	26 (5.5%)	59 (12.4%)
Before index date—HF <sub>rEF</sub>				
Overall	213 (50.4%)	29 (6.9%)	64 (15.1%)	117 (27.7%)
WHFE	69 (32.2%)	11 (5.1%)	50 (23.4%)	84 (39.3%)
NWHFE	144 (68.9%)	18 (8.6%)	14 (6.7%)	33 (15.8%)
After index date—Whole population				
Overall	339 (38.2%)	127 (14.3%)	74 (8.3%)	348 (39.2%)
WHFE	120 (26.2%)	84 (18.3%)	35 (7.6%)	219 (47.8%)
NWHFE	219 (50.9%)	43 (10.0%)	39 (9.1%)	129 (30.0%)
After index date—HF <sub>rEF</sub>				
Overall	154 (33.0%)	75 (16.1%)	36 (7.7%)	201 (43.1%)
WHFE	58 (22.5%)	53 (20.5%)	16 (6.2%)	131 (50.8%)
NWHFE	96 (46.2%)	22 (10.6%)	20 (9.6%)	70 (33.7%)

HF<sub>rEF</sub>, heart failure with reduced ejection fraction; NWHFE, no worsening heart failure event; WHFE, worsening heart failure event. Patients were stratified into the following mutually exclusive groups using the cutpoint of 3000 ng/L for N-terminal pro-B-type natriuretic peptide at the index date: (i) with all values  $< 3000$  ng/L (stable low group); (ii) increase from  $< 3000$  to  $\geq 3000$  ng/L (increased group); (iii) decrease from  $\geq 3000$  to  $< 3000$  ng/L (decreased group); and (iv) with all values  $\geq 3000$  ng/L (stable high group).

the corresponding proportion in NWHFE was 35%, suggesting a measurement in the context of the evaluation for the need of hospitalization, or in preparation of an outpatient visit. Patients with a WHFE were tested twice as frequently compared with those with NWHFE. It can be speculated that, in patients with acute symptoms, NT-proBNP is performed during the differential diagnosis workup before a possible or during an actual hospital admission, or it might be part of the evaluation of HF worsening, or can be measured pre-discharge to better track the trajectory of the patient and establish a post-discharge plan, as recommended by the 2022 American guidelines on HF.<sup>11</sup>

Although NT-proBNP trajectories have been associated with morbidity and mortality in both chronic and acute settings,<sup>12–14</sup> the finding of less testing in patients with NWHFE might highlight a perceived less relevant prognostic role in chronic/stable stages. This could be partly due to the lack of high-level evidence supporting a role for NT-proBNP in guiding treatment, as the GUIDE-IT study did not show any efficacy for the biomarker-guided treatment group compared with usual care in reducing the composite of HF hospitalization and cardiovascular mortality.<sup>15</sup> On the other hand, worsening HF is being increasingly recognized as a distinct phase of HF, as indicated by the higher proportion of patients with a WHFE who have been specifically enrolled in more recent HF trials.<sup>16,17</sup> Consistently, we found an independent association between testing and a WHFE; other independent predictors of testing included surrogates of a more severe HF, that is, use of diuretics and higher heart rate (which predicted testing also in NWHFE), highlighting that in the outpatient setting, NT-proBNP might be measured primarily in those patients with worsening symptoms requiring diuretic therapy. HFpEF was also an independent predictor of testing, which highlights the importance of NT-proBNP to identify HF for differential diagnosis purposes.

Several studies support the role of natriuretic peptide testing. In the St Vincent's Screening to Prevent Heart Failure (STOP-HF) study, patients with cardiovascular risk factors were randomly assigned to receive BNP testing, followed by echocardiography if elevated levels were found, or standard of care.<sup>18</sup> Patients who were tested had lower incidence rates of emergency hospitalization for major cardiovascular events.<sup>18</sup> In the NT-proBNP Selected PreventiOn of cardiac events in a population of diabetic patients without a history of Cardiac disease (PONTIAC) randomized controlled trial, patients with type 2 diabetes and high NT-proBNP free of known structural heart disease were assigned to receive specialist cardiac care with up-titration of RASi and beta-blockers vs. standard care.<sup>19</sup> Receiving RASi and beta-blockers reduced the incidence of cardiovascular hospitalization or death, proving that pre-selection with NT-proBNP is an effective way to discriminate patients who benefit from this management.<sup>19</sup>

Across Europe, NT-proBNP testing increased in the last decade also because of more laboratories offering natriuretic

peptides testing and updating local and international guidelines.<sup>4,20</sup> In a British cohort including data from over 1400 general practices, there was an almost 70-fold increase in NT-proBNP testing, from 0.24 per 1000 person-years in 2004 to 16.24 per 1000 person-years.<sup>21</sup> The increased availability of testing also provides a more precise picture of NT-proBNP levels in the real-world HF population, which might contribute to defining new cut-off values for future trial design. We also assessed different subgroups, to identify characteristics and comorbidities associated with probability of testing and of having increased, decreased, or stable levels. In the aforementioned British study, the median value of NT-proBNP in patients with a confirmed HF diagnosis was lower than in our study (1200 vs. 3000 ng/L), which might be due to patients mainly enrolled in secondary/tertiary care in our study and also to a different prevalence of HFpEF, which generally carries lower NT-proBNP levels.<sup>21</sup> In that study, when selecting patients who were newly diagnosed with HF and therefore had more severe HF, similar proportions had an NT-proBNP > 2000 ng/L compared with our study (57% vs. 62%).<sup>22</sup> In the VICTORIA trial, including patients with worsening HF and EF < 45%, the median NT-proBNP was 2816 ng/L, which is closer to the median in our cohort.<sup>23</sup> In the GALACTIC trial, where HFpEF patients were required to receive HF therapy at optimized doses, the median value was 2000 vs. 4150 ng/L in HFpEF patients in the present cohort, further stressing the importance of treatment implementation.<sup>24</sup> It should be underlined that NT-proBNP levels showed high variability in our study population, being consistently higher in WHFE vs. NWHFE patients, in accordance with the more severe HF in the first vs. the latter. It is remarkable that, in our population at index date, 13% had an NT-proBNP > 14 000 ng/L: Such high levels may require therapy optimization, referral to HF specialists, and consideration of advanced therapy.

We reported number of tests and levels in several subgroups according to EF, sex, age, renal function, and presence of atrial fibrillation. Although NT-proBNP levels might differ, its prognostic value does not seem to differ depending on these factors, as reported among others in the GWG-HF registry,<sup>25</sup> SwedeHF,<sup>26</sup> and the PARADIGM-HF<sup>27</sup> and VICTORIA trials.<sup>28</sup>

When categorizing patients according to changes in NT-proBNP using the median value as cutpoint, roughly 80% of patients had a stable level, either stable low or stable high, regardless of whether the changes were assessed in the 6 ( $\pm 3$ ) months before or after the index date. Similar results were reported in the Valsartan Heart Failure Trial, where NT-proBNP changes from baseline to 4 months were categorized in the same way according to the optimal prognostic cut-off found in the trial (1078 pg/mL), and 86% of patients belonged to the stable categories.<sup>29</sup> Whether changes in NT-proBNP have a stronger prognostic value than single assessments is debated, but they have a recognized role as

surrogate endpoint in clinical trials as they might reflect the use of the tested treatment. In a subgroup analysis of the UPSTEP study, despite morbidity and mortality not being improved by guideline-recommended medical therapy guided by BNP levels, the subgroup of HFrEF patients achieving >30% decrease in BNP had better survival compared with patients not achieving such reduction.<sup>30</sup> NT-proBNP change was the only significant, independent predictor of HF hospitalization and all-cause death in patients with HFrEF in the BIOSTAT-CHF cohort, analysing 30 biomarkers in patients with HFrEF.<sup>31</sup> Patients randomized to high-intensity care in the STRONG-HF trial had a significant benefit in terms of survival and quality of life and a greater reduction in NT-proBNP compared with usual care, regardless of EF.<sup>32</sup> In the present study, there was a strong and independent association between increased and stable NT-proBNP levels and WHFE, which might further stress a role for NT-proBNP in identifying patients approaching a more vulnerable phase of their disease course. These data overall highlight the importance of measuring NT-proBNP in HF clinical practice.

### Strengths and limitations

A major strength was the use of a well-characterized HF cohort with full coverage of NT-proBNP measurements performed during their care. Limitations include the observational study design, which is prone to residual confounding when investigating associations between changes in NT-proBNP and outcomes that might also be affected by (i) immortal bias, as patients needed to have at least two NT-proBNP tests, and (ii) selection bias, as more frequent NT-proBNP measurements might be a surrogate for the severity of HF. Additionally, the results represent clinical practice in the region of Stockholm, but the availability, frequency, and increase of NT-proBNP testing may be highly variable across other locations. As SwedeHF has higher coverage in secondary vs. primary care, it is possible that our results somewhat overestimate the proportion of patients having structured follow-up and being tested. We previously showed that patients enrolled in SwedeHF are more likely male, have younger age, and have higher education and lower all-cause mortality as compared with the general Swedish HF population.<sup>33</sup> Therefore, our results might not be representative of NT-proBNP testing practices in other clinical settings across different regions in Sweden, other European countries, or globally.

The data collection for this study was up to 2018, before the issuing of the latest guidelines and consequent implementation. Therefore, our findings might be partially outdated, especially as they do not mirror the introduction of sodium-glucose co-transporter 2 inhibitors as guideline-directed medical therapy in HF, and randomized controlled tri-

als have shown that these drugs decrease NT-proBNP in both acute and chronic settings.<sup>34–36</sup>

We lacked information on the use of intravenous diuretic treatment, and we consequently defined a WHFE only according to a hospitalization for HF.

### Conclusions

Despite the increase in use of NT-proBNP testing over time, after an HF diagnosis testing is still only performed in half of the patients. Testing occurred more frequently in the context of WHFE, with more severe HF, and seemed performed for differential diagnosis purposes, for example, more commonly in HFpEF, where the diagnosis of HF may be less certain. Stable high and increasing NT-proBNP levels were associated with a WHFE. Overall, our data provide a picture of NT-proBNP levels in a real-world population, which might be useful for future trial design, and highlight the benefits of carrying further implementation of NT-proBNP testing in clinical practice.

### Conflict of interest

G.F. has no conflicts of interest related to this work. She reports, unrelated to the present work, grants from the Swedish Heart and Lung Foundation and the Erling Persson Foundation and personal fees from AstraZeneca and Boehringer Ingelheim. L.B. has no conflicts of interest related to this work. D.L. reports personal fees by Merck & Co., Inc., Rahway, NJ, USA. U.D. has no conflicts of interest related to this work. He reports, unrelated to the present work, grants from Pfizer, Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Boston Scientific, and Roche Diagnostics and honoraria/consultancies from Amgen, Pfizer, and AstraZeneca. L.H.L. has no conflicts of interest related to this work. He reports, unrelated to the present work, grants from AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis, and MSD; consultancies from Vifor, AstraZeneca, Bayer, Pharmacosmos, MSD, Medscape, Sanofi, Lexicon, MyoKardia, Boehringer Ingelheim, Servier, Edwards Life Sciences, and Alleviant; speaker's honoraria from Abbott, Orion Pharma, Medscape, Radcliffe, AstraZeneca, Novartis, Boehringer Ingelheim, and Bayer; patent from AnaCardio; and stock ownership from AnaCardio. G.S. has received funding from Merck & Co., Inc., Rahway, NJ, USA, for conducting the current study. He reports grants and personal fees from Vifor, grants from Boehringer Ingelheim, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants and personal fees from Novartis, grants and personal fees from Cytokinetics, personal fees from Medtronic, personal fees from Teva, personal fees from

TMA, grants from Boston Scientific, grants and personal fees from Pharmacosmos, and grants from Bayer, outside the submitted work. J.J.C. reports grants from Vifor Pharma, AstraZeneca, Novo Nordisk, Amgen, and Astellas, outside the submitted work.

## Funding

This study received support from Merck & Co., Inc., Rahway, NJ, USA, through a grant to Karolinska Institutet.

## Supporting information

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

**Figure S1.** Kernel density curves reporting the number of NT-proBNP tests per year in the overall cohort, in WHFE and NWHFE.

**Figure S2.** Histograms representing the proportions of unique patients who had NT-proBNP testing at the index date and after 14,  $\pm$  30 days,  $\pm$  60 days and  $\pm$  90 days, in the overall and in the HFrEF population.

**Table S1.** Number of NT-proBNP testing within the first 6 months, first and second year after the index date per patient in the overall population.

**Table S2.** Number of NT-proBNP testing within the first 6 months, first and second year after the index date per patient in the HFrEF population.

**Table S3.** Baseline characteristics of unique patients who had NT-proBNP testing at the index date – HFrEF population.

**Table S4.** Independent predictors of NT-proBNP testing at the index date in the overall population regardless of EF.

**Table S5.** Independent predictors of NT-proBNP testing at the index date in the HFrEF population.

**Table S6.** NT-proBNP concentration and distribution at the index date presented as i) median, Q1, Q3, min, max; ii) N(%) per 1000 units increase in the overall population.

**Table S7.** NT-proBNP concentration and distribution at the index date presented as i) median, Q1, Q3, min, max; ii) N(%) per 1000 units increase – HFrEF population.

**Table S8.** Pattern of change regardless of EF before the index: patients were stratified into the following mutually exclusive groups using the cutpoint of 3000 for NT-proBNP at the index date and at 6 ( $\pm$ 3) months prior the index date.

**Table S9.** Pattern of change in HFrEF before the index: patients were stratified into the following mutually exclusive groups using the cutpoint of 3000 for NT-proBNP at the index date and at 6 ( $\pm$ 3) months prior the index date: i) with all values  $<$ 3000 (stable low group); ii) increase from  $<$ 3000 to  $\geq$ 3000 (increased group); iii) decrease from  $\geq$ 3000 to  $<$ 3000 (decreased group); iv) with all values  $\geq$ 3000 (stable high group).

**Table S10.** Pattern of change regardless of EF after the index date: patients were stratified into the following mutually exclusive groups using the cutpoint of 3000 for NT-proBNP at the index date and at 6 ( $\pm$ 3) months after the index date: i) with all values  $<$ 3000 (stable low group); ii) increase from  $<$ 3000 to  $\geq$ 3000 (increased group); iii) decrease from  $\geq$ 3000 to  $<$ 3000 (decreased group); iv) with all values  $\geq$ 3000 (stable high group).

**Table S11.** Pattern of change in HFrEF after the index: patients were stratified into the following mutually exclusive groups using the cutpoint of 3000 for NT-proBNP at the index date and at 6 ( $\pm$ 3) months after the index date: i) with all values  $<$ 3000 (stable low group); ii) increase from  $<$ 3000 to  $\geq$ 3000 (increased group); iii) decrease from  $\geq$ 3000 to  $<$ 3000 (decreased group); iii) with all values  $\geq$ 3000 (stable high group).

**Table S12.** Associations between changes in NTproBNP (categorized as stable low/stable high/increased/decreased) in the 6 months measurement prior to the index and WHFE.

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