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ORIGINAL ARTICLE

N-terminal pro-B-type natriuretic peptide testing patterns in patients with heart failure with reduced ejection fraction

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Abstract

Aims The N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a commonly used biomarker in heart failure for diagnosis and prognostication. We aimed to determine the prevalence of NT-proBNP testing, distribution of NT-proBNP concentrations, and factors associated with receiving an NT-proBNP test in patients with heart failure with reduced ejection fraction (HFrEF), including the subset with a worsening heart failure event (WHFE).

Methods and results This was a retrospective cohort study using two US databases: (i) the de-identified Humana Research Database between January 2015 and December 2018 and (ii) the Veradigm PINNACLE Registry® between July 2013 and September 2017. We included adult patients with a confirmed diagnosis of HFrEF. In each data source, a subgroup of patients with a WHFE was identified, where a WHFE was defined as a heart failure-related hospitalization or receipt of intravenous diuretics. Bivariate and multivariate analyses were conducted to assess factors associated with receiving NT-proBNP testing. In Cohort 1 (n = 249 238), 9.2% of patients with HFrEF and 10.8% of patients with a WHFE received NT-proBNP testing. When restricted to patients with at least one laboratory claim, 11.3% of patients with HFrEF and 13.2% of those with a WHFE received NT-proBNP testing. In Cohort 2 (n = 91 444), 2.3% of patients with HFrEF were tested. Median (inter-quartile range) NT-proBNP concentrations among patients with HFrEF were 1399 (423–4087) pg/mL in Cohort 1 and 394 (142–688) pg/mL in Cohort 2. Median (inter-quartile range) NT-proBNP concentrations in the subset of patients with a WHFE in each cohort were 2209 (740–5894) and 464 (174–783) pg/mL, respectively. In Cohort 1, 13.4% of all HFrEF patients receiving NT-proBNP testing and 18.9% of patients with a WHFE had NT-proBNP values >8000 pg/mL; in Cohort 2, these percentages were 1.0% and 2.5%, respectively.

Conclusions In US clinical practice, NT-proBNP testing was not frequently performed in patients with HFrEF. NT-proBNP concentrations varied across data sources and subpopulations within HFrEF.

Keywords Natriuretic peptide, brain; N-terminal pro-B-type natriuretic peptide; Heart failure; Heart failure with reduced ejection fraction

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Introduction

Heart failure (HF) is a serious health problem with high risks of hospitalization and mortality as well as poor quality of life and high economic burden.[1,2] HF with reduced ejection fraction (HFrEF) is a major form of the HF diagnosis and is accompanied by a high risk for cardiovascular events, particularly when the disease course is progressive.[3] Patients with HFrEF who experience a worsening HF event (WHFE) have poorer outcomes, with a 2 year mortality rate of ~22.5% and a 30 day readmission rate of 56%.[4]

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are released by the heart in response to transmural wall stress and neurohormonal stimulation. BNP and NT-proBNP are commonly used biomarkers in HF for diagnosis and prognostication,[5] and concentrations

of NT-proBNP are associated with important physiological measures in HFrEF such as left ventricular ejection fraction, left atrial volume index, and diastolic function.[6] Increases in the concentration of NT-proBNP over time are associated with deleterious left ventricle remodelling, worse quality of life, and higher risk for death or hospitalization.[7] Recent predictive models identified NT-proBNP as one of the most important predictors of hospital readmission and mortality[8,9] Therefore, clinical practice documents acknowledge the utility of BNP and NT-proBNP as important biomarkers for both diagnosis of HF and assessment of clinical deterioration in HF[10–12] and advise that BNP or NT-proBNP values should be a regular component of an HF patient's medical record and should be updated periodically.[12] Additionally, NT-proBNP has also been used as an important inclusion criterion in pivotal trials of HFrEF treatments to ensure a correct diagnosis and enrich for cardiovascular outcome events.[13–17]

In human plasma and serum, NT-proBNP concentrations are typically higher, likely because of its slower clearance from the circulation.[17] Because NT-proBNP immunoassays use the same antibody for detection, whereas BNP assays use different antibodies, standardization is better for NT-proBNP.[17] Furthermore, age-stratified thresholds of NT-proBNP for HF diagnosis have been verified in clinical trials.[18] We therefore focused on NT-proBNP testing in this study, although we also present results on prevalence of BNP testing.

Patterns and results of NT-proBNP testing in patients with HFrEF in clinical practice are not well characterized, with few studies reporting testing rates or full distributions of NT-proBNP concentrations, especially following a WHFE. The objective of this study was to examine the prevalence of NT-proBNP testing and the distribution of NT-proBNP concentrations in patients with HFrEF, both overall and after a WHFE. A secondary objective was to identify patient characteristics associated with receiving NT-proBNP testing.

Methods

Study design and data sources

This was a retrospective cohort study analysing two sources: (i) the de-identified Humana Research Database (Louisville, KY, USA) and (ii) the Veradigm PINNACLE Registry®. The de-identified Humana Research Database includes claims data for all of Humana's fully insured commercial and Medicare Advantage/Part D membership. The database includes Humana member enrolment and medical, pharmacy, and laboratory data and captures inpatient, outpatient, home care, long-term care, and other care settings. Patients from the de-identified Humana Research Database are referred to in the succeeding text as being from 'all settings'.

The PINNACLE Registry is part of the American College of Cardiology's National Cardiovascular Data Registry® and is the largest outpatient quality improvement registry in the USA, capturing data on coronary artery disease, hypertension, HF, and atrial fibrillation. The PINNACLE Registry collects information on patient demographics, payers, cardiovascular events, vital signs, laboratory orders and results, and medications on a voluntary basis with patients selected at the physicians' discretion. The database used in this study contains HF patients only, and it is linked with Symphony Health's Integrated Dataverse (IDV) pharmacy and medical claims data, which contains physician office medical claims, hospital claims, and pharmacy claims. The medical and hospital claims are pre-adjudicated and are submitted by providers to different types of payers including commercial, Medicare, and Medicaid. The pharmacy claims are final paid claims. Note in the analysis of the PINNACLE/IDV database, NT-proBNP testing and concentrations were only available in the PINNACLE Registry, not in IDV claims, so NT-proBNP values from the PINNACLE/IDV database were from the outpatient setting. Thus, patients from the PINNACLE Registry are referred to in the succeeding text as being from 'the outpatient setting'.

Humana data were accessed for the years 2015–18 (the 2015 data were only used for the baseline characteristics in the analysis of factors associated with receiving NT-proBNP testing) and PINNACLE/IDV data from 1 July 2013 to 30 September 2017. All data were de-identified, and this study was exempt from institutional review board approval.

Study population

Study subjects were identified based on an index diagnosis of HFrEF during the respective study periods. For the de-identified Humana Research Database, inclusion criteria were a diagnosis of HFrEF, age ≥18 years on the diagnosis date, and enrolment in the health plan for at least 30 days both before and after the index diagnosis. HFrEF was defined as (i) at least one inpatient claim or two outpatient claims with International Classification of Diseases, Tenth Revision (ICD-10) codes (I50.2X or I50.4X) or (ii) one outpatient claim with an HF diagnosis using ICD-10 codes (I50.1, I50.2X, I50.3X, I50.4X, I50.8X, I50.9, or I11.0) plus one outpatient claim with an HFrEF diagnosis using ICD-10 codes I50.2X or I50.4X (Supporting Information, *Table S1*). For the PINNACLE Registry data, inclusion criteria were a diagnosis of HFrEF, age ≥18 years on the diagnosis date, and ≥1 medical claim and ≥1 pharmacy claim at least 30 days before and after the diagnosis date. HFrEF was defined as (i) a diagnosis of HF in the PINNACLE Registry plus (ii) an ejection fraction <40% or at least two claims showing an HFrEF diagnosis using the ICD-10 codes I50.2X or I50.4X or ICD-9 code 428.2X in the IDV claims (Supporting Information, *Table S1*). In both data sources, patients with clinical trial participation, a heart transplant, a left ventricular assist de-

vice, adult congenital heart disease, or amyloidosis were excluded. Subjects were followed for at least 30 days after the diagnosis, until either death or the end of the study period. For the analysis of patient characteristics associated with the receipt of NT-proBNP testing, eligible patients needed to have a 1 year baseline period.

In each data source, a subgroup of patients with a WHFE was identified, where a WHFE was defined as an HF-related hospitalization or receipt of intravenous diuretics after the index diagnosis date. HF-related hospitalization was defined as a claim for hospital admission with HF or any inpatient claim with a diagnosis of HF using ICD-10 codes I50.1, I50.2x, I50.3x, I50.4x, I50.8x, I50.9, or I11.0, or ICD-9 codes 402.01, 402.11, 402.91, 428.XX, 404.01, 404.03, 404.11, 404.13, 404.91, or 404.93. Intravenous diuretics were identified by either registry records or procedure codes in claims (J1205, J1940, J3265, S0171, and S9361).

Variable measurement

We assessed the prevalence of NT-proBNP and BNP testing, as well as trends in testing over the course of the study period. Testing was confirmed by the presence of a laboratory result. The NT-proBNP testing around the HFrEF diagnosis was determined within 30 days before and after the index diagnosis. Among those with a post-diagnosis test, the duration from the diagnosis to the first post-diagnosis test and the number of NT-proBNP tests performed after the diagnosis were also measured.

N-terminal pro-B-type natriuretic peptide concentrations were determined for each cohort; these analyses were stratified by age (18–65 and >65 years), sex, inpatient status (for cohorts from all settings), estimated glomerular filtration rate (eGFR; ≤30, >30 to <60, and ≥60 mL/min/1.73 m^2), and New York Heart Association (NYHA) classification (I–II or III–IV; for cohorts from the outpatient registry). If multiple NT-proBNP values were available, the one closest to the first diagnosis date was used for the general HFrEF cohorts and the one closest to the worsening event date was used for patients with a WHFE. Also, for patients with a WHFE, only NT-proBNP testing on or within 365 days following the worsening event date was considered. The analysis by inpatient status applied only to the Humana data because PINNACLE is an outpatient registry. In this analysis, an inpatient was defined as a subject with an NT-proBNP test any time from 2 days before hospital admission to 2 days following discharge. All other subjects were classified as 'non-inpatients'.

N-terminal pro-B-type natriuretic peptide concentrations were also assessed as binary (above vs. below) frequency distributions around cut-offs of 125, 300, 3000, 4000, 5000, and 8000 pg/mL. The cut-off values were derived from guideline-recommended diagnostic cut-offs and previous studies showing a difference in cardiovascular outcomes for patients with NT-proBNP values above vs. below these levels.[9,12,19–22] Among subjects with >1 NT-proBNP test, patterns of test results were defined in terms of these cut-offs with respect to the initial test result. Stable patterns were defined as remaining below (low) or above (high) the cut-off after the first test result. Increased values were below the cut-off initially and above it thereafter. Decreased values were above the cut-off initially and below it thereafter. Fluctuating values varied from below to above the cut point, or vice versa, across three or more test results.

To identify patient characteristics associated with receiving NT-proBNP testing, we used bivariate and multivariate analyses. For this analysis, eligible patients were required to have a 1 year baseline period, and the receipt of NT-proBNP testing was assessed from 30 days before the diagnosis date to any time after diagnosis in the study period. Independent variables included sociodemographic variables [age, gender, and insurance type (commercial and Medicare)], clinical data (heart rate; blood pressure; eGFR; serum levels of sodium, potassium, haemoglobin, HbA1c, low-density and high-density lipoprotein cholesterol, total cholesterol, and creatinine; and BNP testing), co-morbidities (anaemia, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, asthma, coronary artery disease, valvular heart disease, pulmonary hypertension, depression, type 2 diabetes, hyperlipidaemia, hypertension, myocardial infarction, peripheral artery disease, sleep apnoea, stroke, and cancer), medical procedures (cardiac resynchronization therapy, coronary artery bypass grafting, cardiac valve surgery, cardioverter-defibrillator implantation, percutaneous coronary intervention, heart transplantation, and left ventricular assist device implantation), pharmacological treatments for HF (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonist, beta-blocker, digoxin, diuretics, hydralazine, ivabradine, and sacubitril/valsartan) and treatment regimens (monotherapy, dual therapy, triple therapy, other, and none), and healthcare resource utilization (inpatient, outpatient, and emergency room visits). The dependent variable was receipt of NT-proBNP testing within 30 days before the HFrEF diagnosis and any time after the diagnosis date. These analyses were conducted only in the de-identified Humana Research Database because of the comparatively small number of patients receiving an NT-proBNP test in the PINNACLE Registry data and the large number of missing values for some patient characteristics of interest.

Statistical analysis

Prevalence of NT-proBNP testing, overall and around the diagnosis date, and distributions of NT-proBNP concentrations are presented as numbers and percentages. NT-proBNP concentrations are presented as medians and inter-quartile ranges (IQRs). The number of days to the first

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post-diagnosis test was assessed as both a mean with its standard deviation and a median with its range. The number of NT-proBNP tests in Years 1–3 after diagnosis is presented as the mean and standard deviation.

In stratified analyses of NT-proBNP concentrations, the comparison of NT-proBNP values across groups was based on a Wilcoxon rank-sum test or non-parametric one-way ANOVA. Patient characteristics were assessed for association with receiving NT-proBNP testing using bivariate and multivariate analyses. Bivariate analyses were compared by Student's *t*-tests for continuous variables and by χ^2 tests for categorical variables. Multiple logistic regression was utilized for multivariate analyses. Because of the large number of missing values for laboratory results, these clinical variables were not included in the multivariate analyses.

Because the de-identified Humana Research Database only captures laboratory data from part of their laboratory and data vendors, we also conducted sensitivity analyses using the subset of patients with one or more laboratory claims in the study period.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). *P* values <0.05 were considered statistically significant.

Results

Proportion of patients receiving N-terminal pro-B-type natriuretic peptide testing

Of the 249 238 patients with HFrEF from all settings, 22 830 (9.2%) had an NT-proBNP test during 2016–18; 10.8% of patients with a WHFE received a test in the study period (*Table 1*). When restricted to patients with at least one laboratory claim, 11.3% of patients with HFrEF and 13.2% of those with a WHFE received NT-proBNP testing (data not shown). In the outpatient registry cohort, all patients with HFrEF and the subset of patients with a WHFE both received NT-proBNP testing at a rate of 2.3% (*Table 1*). Testing prevalence increased by 1–2 percentage points over the 3 year analysis period in all of these cohorts (*Figure 1*). For the purposes of comparison, the testing prevalence and trends for BNP are shown in *Table 1* and *Figure 1*.

Proportions of patients undergoing N-terminal pro-B-type natriuretic peptide testing at different time points

In both data sources, about one-third of patients with an NT-proBNP test received it around the time of their HFrEF diagnosis (36.9% in the all-setting cohort and 30.6% in the outpatient registry cohort), but the majority received the test after the diagnosis (90.4% and 88.0%, respectively; *Table 2*).

For those who had NT-proBNP testing after the HFrEF diagnosis, the median number of days from diagnosis to NT-proBNP testing was 118 for both cohorts, and patients received an average of 1.7–2.1 tests in the first year across both cohorts. This number slightly decreased in the second and third years following the diagnosis. Results for subgroups with a WHFE were not substantially different.

N-terminal pro-B-type natriuretic peptide concentrations and distribution

Figure 2 shows the distribution of NT-proBNP concentrations in both data sources. Most patients with HFrEF from all settings had NT-proBNP concentrations >1000 pg/mL, whereas most patients with HFrEF from the outpatient setting had concentrations <1000 pg/mL.

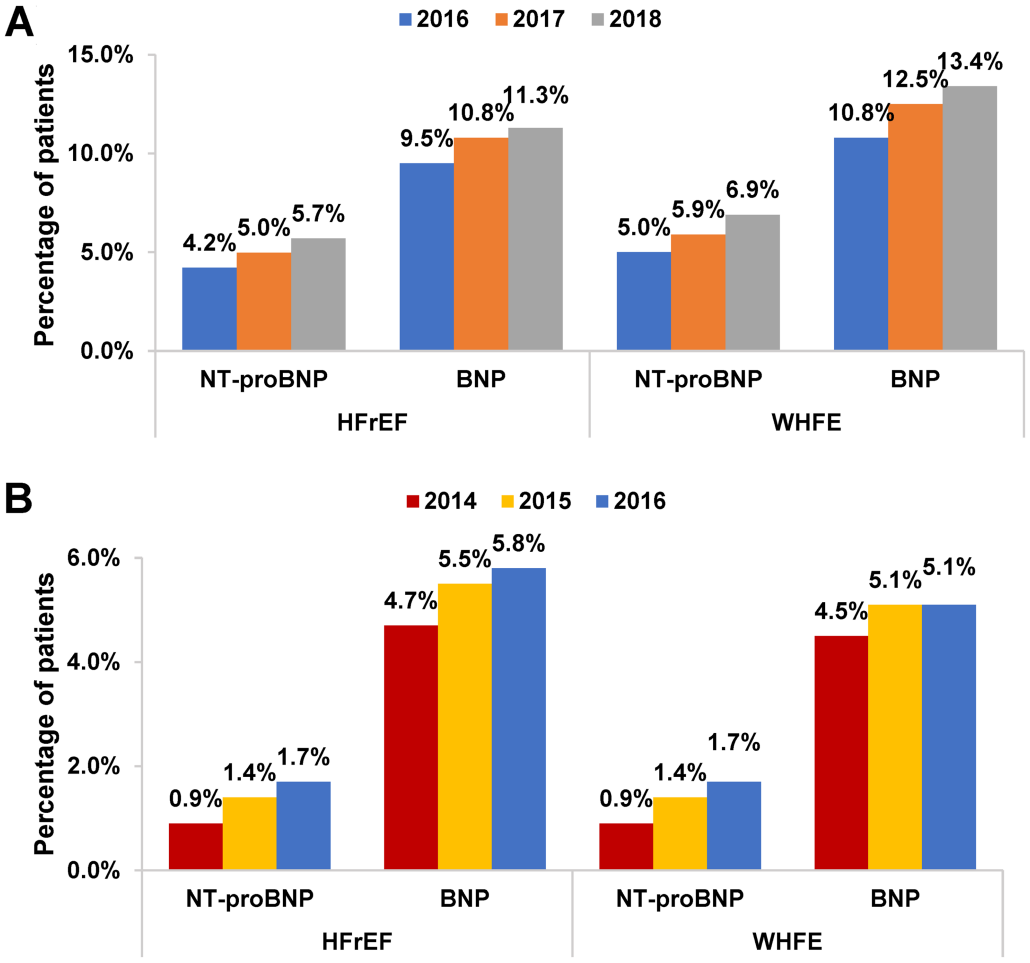
Median (IQR) NT-proBNP concentrations around the HFrEF diagnosis were 1399 (423–4087) pg/mL in patients with HFrEF from all settings and 394 (142–688) pg/mL in patients with HFrEF from the outpatient setting (*Table 3*). Median (IQR) NT-proBNP concentrations tested following the event in patients with a WHFE were higher than the concentrations for HFrEF patients tested around diagnosis: 2209 (740–5894) in the all-setting cohort and 464 (174–783) pg/mL in the outpatient registry cohort (*Table 3*). In patients with HFrEF from all settings, 91.6%, 80.7%, 32.0%, 25.5%, 21.1%, and 13.4% had NT-proBNP concentrations above 125, 300, 3000, 4000, 5000, and 8000 pg/mL, respectively (*Table 3*). At each cut-off, the percentage of patients with a WHFE from all settings was higher (95.8%, 89.0%, 41.7%, 34.2%, 28.6%, and 18.9%, respectively). Few patients with HFrEF from the outpatient setting had NT-proBNP concentrations above the higher cut-offs (3000, 4000, 5000, and 8000 cut-offs: 3.4%, 2.7%, 2.3%,

Table 1 Prevalence of NT-proBNP and BNP testing

	Patients with HFrEF from all settings[a] (*N* = 249 238)	Patients with a WHFE from all settings[a] (*N* = 166 892)	Patients with HFrEF from the outpatient setting[b] (*N* = 91 444)	Patients with a WHFE from the outpatient setting[b] (*N* = 50 093)
NT-proBNP testing, *N* (%)	22 830 (9.2%)	18 015 (10.8%)	2108 (2.3%)	1141 (2.3%)
BNP testing, *N* (%)	48 088 (19.3%)	36 794 (22.0%)	7649 (8.4%)	3847 (7.7%)

BNP, B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHFE, worsening heart failure event.
[a]The de-identified Humana Research Database.
[b]PINNACLE Registry.

Figure 1 Trends in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) testing. The data points show the percentages of patients with heart failure with reduced ejection fraction (HFrEF) and the subgroup of patients with a worsening heart failure event (WHFE) with an NT-proBNP or BNP test in years (A) 2016–18 for cohorts from the de-identified Humana Research Database (all settings) and (B) 2014–16 for cohorts from the PINNACLE Registry (outpatient setting).



and 1.0%, respectively), but the percentage of patients was again higher in the subgroup of patients with a WHFE (3000, 4000, 5000, and 8000 cut-offs: 7.1%, 6.0%, 5.1%, and 2.5%, respectively; *Table 3*).

Stratified analyses of patients with HFrEF and the WHFE subgroup from all settings showed that NT-proBNP concentrations were higher in older patients (>65 vs. 18–64 years), inpatients (vs. non-inpatients), and in patients with lower eGFR (all $P < 0.001$; Supporting Information, *Table S2*). In patients with HFrEF from the outpatient setting, higher NT-proBNP concentrations were observed in HFrEF patients with older age, higher NYHA functional class (III–IV vs. I–II), and lower eGFR (Supporting Information, *Table S3*). Similar trends were observed in the WHFE subgroup from the outpatient setting except that NYHA functional class was no longer significant.

Among patients from all settings who had NT-proBNP tested, inpatient status was assigned to 53.0% of all patients with HFrEF and 65.2% of patients with a WHFE (Supporting Information, *Table S2*). Among these inpatients, NT-proBNP concentrations were higher at admission than at discharge, which was observed in both the overall population with HFrEF and the subgroup with a WHFE (Supporting Information, *Table S4*).

Patterns of test results

In patients with HFrEF from all settings, most patients had an initial test result below 4000 pg/mL and maintained concentrations below this cut-off in subsequent tests (57.7%; *Table 4*). However, a small proportion of this cohort had NT-proBNP concentrations consistently above this cut-off over multiple tests (15.7%) or concentrations that increased from the initial test to subsequent tests (9.9%; *Table 4*). At each cut-off, stable high NT-proBNP concentrations were

Table 2 Proportion of patients undergoing NT-proBNP testing at different time points and number of tests at different time points[a]

	Patients with HFrEF from all settings[b] (*N* = 22 830)	Patients with a WHFE from all settings[b] (*N* = 18 015)	Patients with HFrEF from the outpatient setting[c] (*N* = 2108)	Patients with a WHFE from the outpatient setting[c] (*N* = 1141)
Within 30 days before and after the HFrEF diagnosis, *n* (%)	8426 (36.9%)	6733 (37.4%)	644 (30.6%)	304 (26.6%)
After HFrEF diagnosis, *n* (%)	20 640 (90.4%)	16 625 (92.3%)	1855 (88.0%)	1052 (92.2%)
Days to first post-diagnosis test, mean (SD)[d]	236.5 (274.6)	231.0 (271.7)	230.3 (270.6)	245.6 (274.7)
Days to first post-diagnosis test, median[d]	118	111	118	133
NT-proBNP tests in Year 1, mean (SD)	2.1 (2.2)	2.3 (2.3)	1.7 (1.4)	1.8 (1.5)
NT-proBNP tests in Year 2, mean (SD)	2.0 (2.1)	2.2 (2.2)	1.5 (1.1)	1.5 (1.1)
NT-proBNP tests in Year 3, mean (SD)	2.0 (2.2)	2.1 (2.3)	1.5 (1.1)	1.5 (1.0)

HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; WHFE, worsening heart failure event.
[a]*N* (%) values are numbers of patients and percentages, whereas mean (SD) and median values are numbers of tests.
[b]The de-identified Humana Research Database.
[c]PINNACLE Registry.
[d]Among patients tested after diagnosis (*n* = 20 640 from all settings; *n* = 1855 from the outpatient setting).

Figure 2 N-terminal pro-B-type natriuretic peptide (NT-proBNP) value distribution. (A) All eligible patients with heart failure with reduced ejection fraction (HFrEF) in the de-identified Humana Research Database, and the subgroup with a worsening heart failure event (WHFE). (B) All patients with HFrEF in the PINNACLE Registry, and the subgroup with a WHFE.

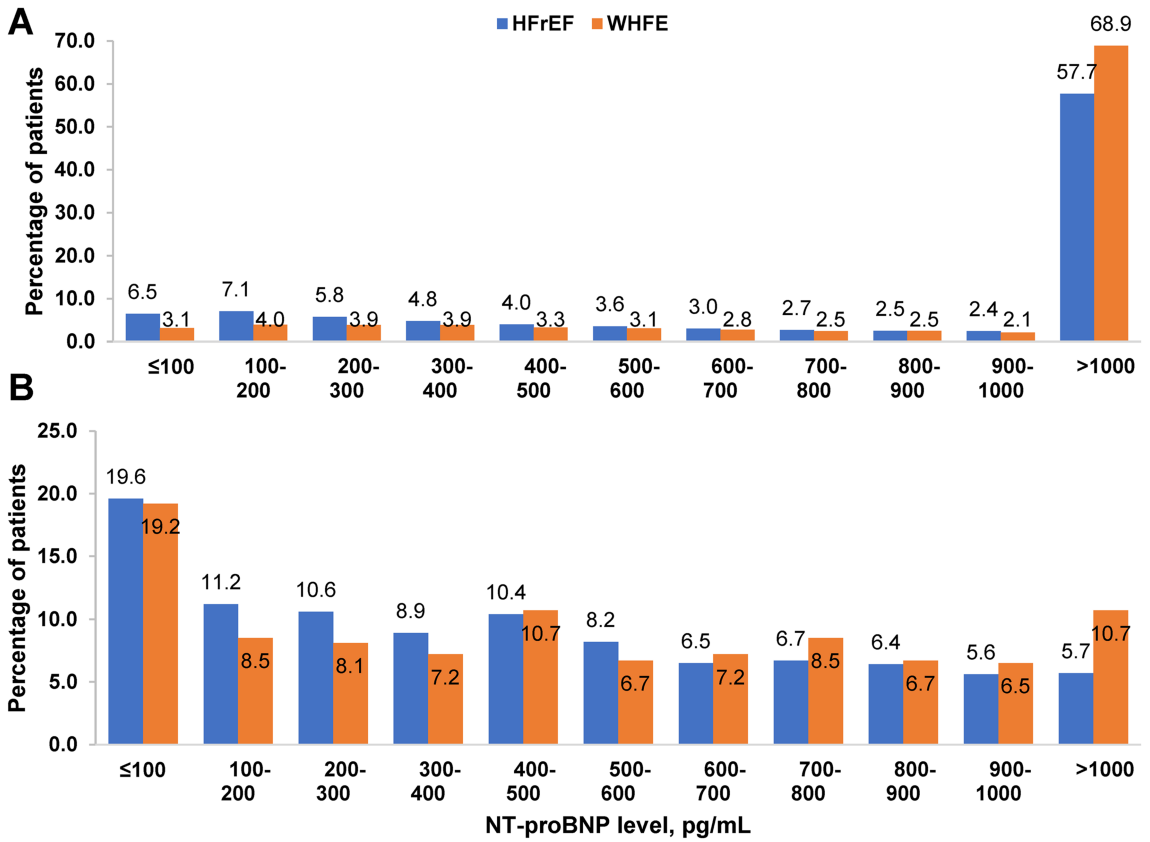


Table 3 NT-proBNP concentrations and distribution[a]

	Patients with HFrEF from all settings[b] (*N* = 22 830)	Patients with a WHFE from all settings[b] (*N* = 9787)	Patients with HFrEF from the outpatient setting[c] (*N* = 2108)	Patients with a WHFE from the outpatient setting[c] (*N* = 553)
Median (IQR) NT-proBNP (pg/mL)	1399 (423–4087)	2209 (740–5894)	394 (142–688)	464 (174–783)
NT-proBNP distribution, *N* (%)				
>125 pg/mL	20 918 (91.6)	9373 (95.8)	1619 (76.8)	432 (78.1)
>300 pg/mL	18 426 (80.7)	8709 (89.0)	1235 (58.6)	355 (64.2)
>3000 pg/mL	7312 (32.0)	4084 (41.7)	72 (3.4)	39 (7.1)
>4000 pg/mL	5820 (25.5)	3349 (34.2)	57 (2.7)	33 (6.0)
>5000 pg/mL	4811 (21.1)	2802 (28.6)	49 (2.3)	28 (5.1)
>8000 pg/mL	3058 (13.4)	1851 (18.9)	22 (1.0)	14 (2.5)

HFrEF, heart failure with reduced ejection fraction; IQR, inter-quartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHFE, worsening heart failure event.
[a]*N* (%) values are numbers of patients and percentages. The testing closest to the first diagnosis date was used for the general HFrEF cohorts, and the one closest to the worsening event date and on or within 365 days following the event was used for patients with a WHFE.
[b]The de-identified Humana Research Database.
[c]PINNACLE Registry.

more frequent among patients with a WHFE than the overall population of patients with HFrEF, but still the majority of patients with a WHFE had stable low NT-proBNP concentrations. Almost all patients with HFrEF from the outpatient setting were stably below the 8000 pg/mL cut-off (96.5%), while only about three-fourths (73.9%) of patients with HFrEF from all settings were classified this way. The majority of patients with a WHFE had NT-proBNP concentrations consistently below 8000 pg/mL (68.2% in the all-setting cohort and 94.2% in the outpatient cohort).

Patient characteristics associated with receiving N-terminal pro-B-type natriuretic peptide testing

Patient characteristics (sociodemographic variables, clinical data, co-morbidities, medical procedures, pharmacological treatments for HF and treatment regimens, and healthcare resource utilization) associated with NT-proBNP testing in bivariate analyses are shown in Supporting Information, *Table S5*. Multiple logistic regression results were generally similar across cohorts from all settings (*Figure 3*: Cohort 1 = all eligible patients with HFrEF in the de-identified Humana Research Database; Cohort 2 = the subgroup with a WHFE in the de-identified Humana Research Database; Cohort 3 = all eligible patients with HFrEF in the de-identified Humana Research Database with ≥1 laboratory claim; and Cohort 4 = the subgroup with a WHFE in the de-identified Humana Research Database with ≥1 laboratory claim). The results consistently showed that female sex increased the odds of NT-proBNP testing and that having Medicare insurance increased the odds of receiving NT-proBNP testing compared with commercial insurance. With the exception of Cohort 1 (all patients with HFrEF), all models showed that patients receiving BNP testing were significantly less likely to receive NT-proBNP testing. The majority of co-morbidities were consistently found to significantly increase the odds of receiving NT-proBNP testing, including chronic obstructive pulmonary disease, pulmonary hypertension, type 2 diabetes, hyperlipidaemia, hypertension, peripheral artery disease (except in patients in Cohort 4), and sleep apnoea. On the other hand, there were certain co-morbidities significantly associated with lower likelihood of receiving NT-proBNP testing, including cancer, myocardial infarction, anaemia (except in Cohort 1), and depression (except in Cohort 1). The more pharmacological treatments patients had for HFrEF, the less likely patients were to receive NT-proBNP testing.

Discussion

To have a more comprehensive assessment of NT-proBNP testing in US clinical practice, we utilized two of the best available data sources in the USA, the PINNACLE Registry as well as a claims database of a major commercial and Medicare Advantage insurer in the USA. This study found that, although natriuretic peptide testing has been recommended as an important biomarker for diagnosis and prognosis in HF, its utilization was still strikingly low in US clinical practice, especially for NT-proBNP, which is a relatively more stable and comparable testing. NT-proBNP concentrations varied across different data sources, with lower levels in an outpatient registry (PINNACLE) than a general, mixed-setting database (the de-identified Humana Research Database). NT-proBNP concentrations were higher in the inpatient setting than the non-inpatient setting and were higher in patients with a WHFE. Overall, the percentages of patients with very high NT-proBNP (>8000 pg/mL), both overall and in the subgroups with a WHFE, were small, and the majority of patients had stable low NT-proBNP concentrations. Our study findings may provide important guidance on NT-proBNP utilization in clinical practice and may have research implications as NT-proBNP is used as an inclusion criterion in clinical trials.

With a growing emphasis on natriuretic peptides for longitudinal patient monitoring,[12] along with possible interactions

Table 4 Patterns of NT-proBNP test results[a]

	Patients with HFrEF from all settings[b] (*N* = 11 893)	Patients with a WHFE from all settings[b] (*N* = 4693)	Patients with HFrEF from the outpatient setting[c] (*N* = 932)	Patients with a WHFE from the outpatient setting[c] (*N* = 223)
Cut point: 125 pg/mL				
Stable low	322 (2.7)	66 (1.4)	114 (12.2)	20 (9.0)
Increased	422 (3.6)	78 (1.7)	51 (5.5)	8 (3.6)
Decreased	301 (2.5)	88 (1.9)	71 (7.6)	18 (8.1)
Stable high	10 466 (88.0)	4388 (93.5)	631 (67.7)	165 (74.0)
Fluctuated	382 (3.2)	73 (1.6)	65 (7.0)	12 (5.4)
Cut point: 300 pg/mL				
Stable low	1010 (8.5)	223 (4.8)	242 (26.0)	46 (20.6)
Increased	795 (6.7)	134 (2.9)	99 (10.6)	18 (8.1)
Decreased	552 (4.6)	213 (4.5)	104 (11.2)	29 (13.0)
Stable high	8780 (73.8)	3945 (84.1)	401 (43.0)	117 (52.5)
Fluctuated	756 (6.4)	178 (3.8)	86 (9.2)	13 (5.8)
Cut point: 3000 pg/mL				
Stable low	5992 (50.4)	2011 (42.9)	849 (91.1)	188 (84.3)
Increased	1216 (10.2)	376 (8.0)	15 (1.6)	4 (1.8)
Decreased	858 (7.2)	469 (10.0)	15 (1.6)	5 (2.2)
Stable high	2498 (21.0)	1423 (30.3)	28 (3.0)	20 (9.0)
Fluctuated	1329 (11.2)	414 (8.8)	25 (2.7)	6 (2.7)
Cut point: 4000 pg/mL				
Stable low	6867 (57.7)	2367 (50.4)	860 (92.3)	195 (87.4)
Increased	1174 (9.9)	384 (8.2)	16 (1.7)	3 (1.3)
Decreased	751 (6.3)	425 (9.1)	12 (1.3)	5 (2.2)
Stable high	1866 (15.7)	1104 (23.5)	22 (2.4)	17 (7.6)
Fluctuated	1235 (10.4)	413 (8.8)	22 (2.4)	3 (1.3)
Cut point: 5000 pg/mL				
Stable low	7519 (63.2)	2648 (56.4)	877 (94.1)	200 (89.7)
Increased	1111 (9.3)	381 (8.1)	14 (1.5)	4 (1.8)
Decreased	650 (5.5)	381 (8.1)	8 (0.9)	5 (2.2)
Stable high	1477 (12.4)	896 (19.1)	15 (1.6)	10 (4.5)
Fluctuated	1136 (9.6)	387 (8.3)	18 (1.9)	4 (1.8)
Cut point: 8000 pg/mL				
Stable low	8794 (73.9)	3200 (68.2)	899 (96.5)	210 (94.2)
Increased	912 (7.7)	330 (7.0)	13 (1.4)	3 (1.3)
Decreased	466 (3.9)	299 (6.4)	6 (0.6)	3 (1.3)
Stable high	843 (7.1)	533 (11.4)	2 (0.2)	1 (0.4)
Fluctuated	878 (7.4)	331 (7.1)	12 (1.3)	6 (2.7)

HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHFE, worsening heart failure event.

[a]Among those with >1 test result. All values are presented as *n* (%), where *n* is the number of patients. See the Methods section for definitions of the different patterns.

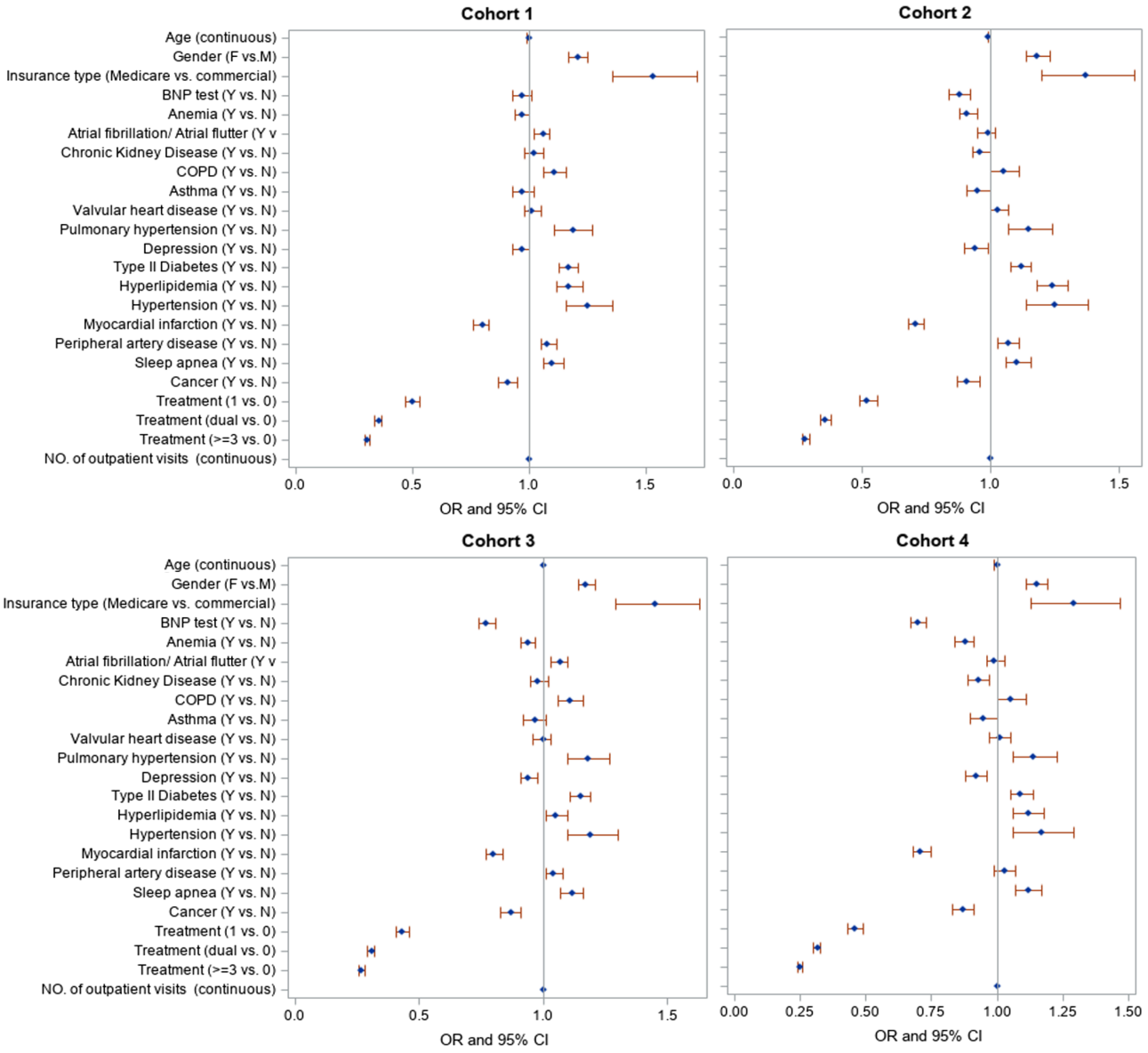
[b]The de-identified Humana Research Database.

[c]PINNACLE Registry.

between BNP or NT-proBNP and response to therapies for HF,[19–21,23] our results provide important insights, particularly because few previous studies have reported the prevalence of NT-proBNP testing. In an analysis of the American Heart Association's 'Get with the Guidelines' cohort, just 9% of over 60 000 hospitalized HF patients were tested for NT-proBNP in 2005–08.[24] An analysis of the ADHERE-AP registry (2006–08), which included over 10 000 hospitalized HF patients from the Asia-Pacific region, found that 8.5% had an NT-proBNP measurement.[25] Some smaller real-world data studies have reported higher rates of NT-proBNP testing: 22.7% among 1509 patients in the Taiwan Society of Cardiology HF registry (2013–15),[26] and 65.1% of 1527 patients in the Korean HF registry (2005–09).[27] Variations in testing rates may reflect changes over time, different practice patterns across different geographical regions, different population composition, or different data coverage. Although BNP and NT-proBNP may be used in a mutually exclusive way in different healthcare settings or geographical regions, our data showed that the prevalence of all natriuretic peptide testing was around 30% in HFrEF patients in US clinical practice. Even if our findings underestimate the testing prevalence due to data availability limitations, the majority of studies with large sample sizes, including ours, show that NT-proBNP was not frequently tested in routine practice for patients with HFrEF.

The NT-proBNP concentrations reported in cohorts from all settings were comparable with other large HFrEF populations worldwide in real-world studies.[28–31] We observed few HF patients above 8000 pg/mL, and only a small percentage had stable high NT-proBNP with respect to this cut-off. Moreover, we also found that patients with common co-morbidities and hospitalized patients were more likely to

Figure 3 Multivariate analysis of patient characteristics associated with the receipt of N-terminal pro-B-type natriuretic peptide testing. Study cohorts in the de-identified Humana Research Database are numbered as follows: Cohort 1 = all eligible patients with heart failure with reduced ejection fraction (HFrEF); Cohort 2 = the subgroup with a worsening heart failure event (WHFE); Cohort 3 = all eligible patients with HFrEF with ≥1 laboratory claim; and Cohort 4 = the subgroup with a WHFE with ≥1 laboratory claim. BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; F/M, female/male; OR, odds ratio; Y/N, yes/no.



receive NT-proBNP testing, which may lead to increased NT-proBNP concentrations reported. Because <15% of patients received NT-proBNP testing, it is likely that we overestimated the NT-proBNP concentrations, and the true population would have lower levels than those reported here if everyone got tested.

In this study, NT-proBNP concentrations were higher in patients with a WHFE than those at diagnosis in the general HFrEF population. Our study findings also corroborate the previously described relationship of NT-proBNP concentration with age[32–34] and eGFR.[34] The link between NT-proBNP levels and eGFR is likely due to a combination of reduced clearance of natriuretic peptides and increased biomarker release due to greater prevalence of structural heart abnormalities and congestion in HF patients with reduced kidney function.[12] Also this study adds to these findings a description of trends in NT-proBNP concentrations by inpatient status, which confirmed that inpatients have higher NT-proBNP concentrations.

Moreover, we found in the inpatient setting that NT-proBNP concentrations at admission were higher than those at discharge. The observation that NT-proBNP was highest during the hospital stay may have been because those who had NT-proBNP tested during their hospital stay would have had longer lengths of stay as per our definition and classification.

Consistent with measurement in different venues,[35] we observed much lower NT-proBNP concentrations in the PINNACLE Registry than the de-identified Humana Research Database (median 394 vs. 1399 pg/mL for HFrEF patients). The basic difference between these two data sources is that the PINNACLE Registry is derived from outpatients, whereas the de-identified Humana Research Database includes claims from all settings, with a majority of NT-proBNP tests occurring in the inpatient setting. Because our data indicate that NT-proBNP concentrations are higher in inpatient settings than non-inpatient settings (see Supporting Information, *Table S2*), this may explain the higher NT-proBNP concentrations we observed in the HFrEF and WHFE cohorts from the de-identified Humana Research Database. In addition, the PINNACLE data underwent truncation of values over 35 000 pg/mL, maybe due to lack of dilution above the upper reference limit. Furthermore, NT-proBNP testing in the PINNACLE Registry was voluntarily reported by physicians, which may mean that NT-proBNP testing is under-reported, limiting the representativeness of NT-proBNP concentrations in the registry data.

This study also assessed factors associated with receiving NT-proBNP testing, which may provide evidence in support of targeted interventions to address the underuse of NT-proBNP testing in specific subsets of patients with HFrEF. Men were much less likely to receive NT-proBNP testing than women. Some common co-morbidities may increase the possibility of receiving testing, while other co-morbidities (e.g., cancer and anaemia) may have the opposite effect. Moreover, an increase in the number of HFrEF pharmacotherapies was associated with lower likelihood of receiving NT-proBNP testing, which implies that NT-proBNP was more often used for diagnosis and prognosis rather than guiding treatment decisions in clinical practice. However, the factors assessed in this study were baseline characteristics, and future longitudinal research is needed on factors associated with receiving NT-proBNP testing over a longer trajectory. In addition, there was also a significant variation with insurance type of the likelihood of receiving NT-proBNP testing. Overall, the cost for NT-proBNP testing may not be considered prohibitive as it is widely covered by insurance, but there are some coverage limitations that may prevent the utilization for certain patients. For US patients without insurance (~9.2% of the total US population)[36] or among those with poor insurance coverage, the full price of the testing may be a significant burden, which may, in part, explain the low utilization of NT-proBNP testing in US clinical practice reported here. In contrast, in Sweden, almost 90% of HFrEF patients receive NT-proBNP testing.[37] Possible explanations for the high utilization in Sweden include universal health coverage, physicians relying on NT-proBNP for HF diagnosis, and physicians routinely utilizing testing in clinical practice. Similarly, the cost for NT-proBNP testing may not be a barrier in the UK, which also has universal health coverage. The National Institute for Health and Care Excellence guideline 2018 update recommended NT-proBNP testing as a crucial step in HF diagnosis and as a consideration for monitoring HFrEF patients aged $<$75 years and with an eGFR above 60 mL/min/1.73 m^2.[38,39] This guideline may further influence the utilization of the testing in clinical practice in the UK.

This study had some limitations. We used two disparate data sources that cannot be directly compared, and the PINNACLE Registry is limited by voluntary reporting of participating physicians in the outpatient setting, which may not reflect the true NT-proBNP distribution in all settings in clinical practice. There are also some limitations regarding the de-identified Humana Research Database, which captures laboratory data from selected laboratory and data vendors, so it does not have 100% coverage for laboratory results. To alleviate this issue, we conducted sensitivity analyses to include only patients with laboratory claims during the study period. Moreover, the measurement of patterns of NT-proBNP test results may have introduced immortal time bias, because patients needed to have at least two NT-proBNP tests ($\geq$3 for the 'fluctuated' group). Also, some of the study variables were defined specifically for our analysis, namely, inpatient status and the corresponding admission/in-hospital/discharge periods, and thus, there may be misclassification. Although we assessed patient characteristics associated with receiving NT-proBNP testing, the retrospective nature of the study precludes an examination of causality. Additionally, the current study design limits our perspective to a relatively short time period and a somewhat static picture of the patient trajectory. Future research is warranted on a more detailed delineation of NT-proBNP changes in the patient trajectory. Finally, further research may be needed on other HF populations, BNP distribution, and the prognostic value of NT-proBNP.

In conclusion, we found that NT-proBNP was not frequently performed in patients with HFrEF in the USA. NT-proBNP concentrations varied across different data sources and HF populations. There were small percentages of patients, both overall and in the subgroup with a WHFE, with very high NT-proBNP ($>$8000 pg/mL), and the majority of patients had stable low NT-proBNP. Because of the variation across settings, more evidence may be warranted before relying on NT-proBNP testing and concentrations for treatment decisions in clinical practice.

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Conflict of interest

X.T., L.Y., J.E.B., P.B., and D.L. are employees of Merck Sharp and Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and stockholders in Merck & Co., Inc., Kenilworth, NJ, USA. M.Y. was an employee of Merck Sharp and Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, at the time of conducting the study. J.L.J. has received consulting fees or advisory and funding grants from Roche Diagnostics, Siemens Diagnostics, Abbott Diagnostics, and Merck

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Supporting information

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

Table S1. Definitions of heart failure with reduced ejection fraction and worsening heart failure event using ICD and procedure codes.

Table S2. NT-proBNP values and distribution in patients with HFrEF and with a WHFE from all settings, stratified by age, gender, setting, and estimated glomerular filtration rate.

Table S3. NT-proBNP values and distribution in patients with HFrEF and with a WHFE from the outpatient registry, stratified by age, gender, functional classification, and estimated glomerular filtration rate.

Table S4. NT-proBNP values and distribution in the inpatient setting.

Table S5. Bivariate analysis of patient characteristics associated with receiving NT-proBNP testing [A].

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