ORIGINAL RESEARCH

Usefulness of B-Type Natriuretic Peptide for Predicting the Risk of Stroke in Patients With Heart Failure With Preserved Ejection Fraction

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BACKGROUND: B-type natriuretic peptide (BNP) is a well-known biomarker for prognosis in heart failure with patients with preserved ejection fraction. However, the clinical predictive ability of BNP for the risk of stroke in HFpEF is not clear.

METHODS AND RESULTS: A total of 799 patients with HFpEF from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial were included. Association of baseline BNP with risk of stroke was assessed using the Cox proportional hazard model. The discriminatory ability of BNP was expressed using the C index. The improvement in 5-year stroke prediction was assessed by C statistic, categorical net reclassification improvement index, and relative integrated discrimination improvement. A total of 34 (4.3%) patients among the 799 patients with HFpEF experienced stroke events over a median of 2.85 years of follow-up. The stroke group showed a higher BNP level than the nonstroke group (375 pg/mL versus 241 pg/mL, respectively; $P=0.006$). Higher BNP levels were associated with increased risk of stroke after multivariable adjustment (hazard ratio, 3.29 [95% CI, 1.51–7.16]) and had a moderate performance for stroke prediction (C index, 0.67). Adding BNP to $CHADS_2$/CHA_2DS_2-VASc/R_2CHADS_2 scores improved their predictive value for stroke ($CHADS_2$: C index, 0.67; BNP+$CHADS_2$: C index, 0.77; net reclassification improvement, 40.9%; integrated discrimination improvement, 3.0%; CHA_2DS_2-VASc: C index, 0.64; BNP+CHA_2DS_2-VASc: C index, 0.74; net reclassification improvement, 41.4%; integrated discrimination improvement, 2.2%; R_2CHADS_2: C index, 0.70; BNP+R_2CHADS_2: C index, 0.78; net reclassification improvement, 40.9%; integrated discrimination improvement, 3.2%).

CONCLUSIONS: BNP is associated with an increased risk of stroke in patients with HFpEF and may be a valuable biomarker for stroke prediction in HFpEF.

Key Words: B-type natriuretic peptide ■ heart failure ■ risk prediction ■ stroke

Heart failure (HF) with preserved ejection fraction (HFpEF) is a highly complex clinical syndrome with a high prevalence with increasing age.[1] Stroke is considered a devastating outcome, with high levels of mortality and morbidity.[2] Epidemiological studies from several cohorts have shown that thrombus formation and stroke incidence in patients with HFpEF are similar or somewhat higher than those in patients with

CLINICAL PERSPECTIVE

What Is New?

- We first evaluated the predictive value of B-type natriuretic peptide for risk of stroke in patients with heart failure with preserved ejection fraction.
- Higher B-type natriuretic peptide levels are associated with increased risk of stroke and have a moderate performance for stroke prediction in heart failure with preserved ejection fraction.
- Addition of B-type natriuretic peptide to CHA_2DS_2/CHA_2DS_2-VASc/R_2CHADS_2 scores significantly improved their stroke prediction in heart failure with preserved ejection fraction.

What Are the Clinical Implications?

- The current findings suggest that B-type natriuretic peptide might be a potential valuable biomarker for stroke prediction in heart failure with preserved ejection fraction.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
IDI	integrated discrimination improvement
NRI	net reclassification improvement index
NYHA	New York Heart Association
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

reduced ejection fraction.[1,3–5] Thus, the prediction of stroke in HFpEF remains an urgent clinical issue.

Several stroke risk scores, such as the $CHADS_2$ and CHA_2DS_2-VASc, have been developed to predict stroke in patients with atrial fibrillation (AF).[6] AF and HF, the vicious twins, often coexist and independently contribute to poor outcomes.[7,8] However, as we previously reported, the established stroke risk scores including CHA_2DS_2-VASc and anticoagulation and risk factors in atrial fibrillation did not work well.[9] Moreover, although HFpEF is associated with the development of AF, concomitant AF cannot directly explain the risk of systemic thromboembolic events in patients with HFpEF. These observations supported the opinion raised by some authors that HFpEF itself is the substrate for stroke.[10]

B-type natriuretic peptide (BNP) is a well-known biomarker for the presence and severity of HF and prognosis of patients with HF.[11,12] In regard to HFpEF, BNP has been statistically significantly associated with adverse outcomes, such as all-cause mortality and hospitalization for HF.[13,14] Elevated plasma BNP levels were shown to predict the risk of stroke in the general population in several community-based longitudinal cohorts.[15,16] More recently, in patients with chronic HF, the use of BNP to predict the occurrence of stroke has also been reported.[17] Given this background, by using the data set from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, a large, randomized controlled trial that investigated the effect of spironolactone in HFpEF, we performed a secondary analysis to (1) assess the association between BNP and the risk of stroke and (2) determine whether the addition of BNP to existing stroke risk scores ($CHADS_2$/CHA_2DS_2-VASc/R_2CHADS_2) could provide a better prediction of the risk of stroke in patients with HFpEF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We used the TOPCAT trial data set, a multicenter, international, randomized, double-blind, placebo-controlled phase III trial of the spironolactone at 233 sites in 6 countries. Briefly, this trial enrolled 3445 patients with HFpEF from the Americas and Russia/Georgia, with (1) an age of 50 years or older, (2) left ventricular ejection fraction ≥45% and at least one sign and symptom of HF, (3) controlled systolic blood pressure, a serum potassium level <5.0 mmoL/L, and an estimated glomerular filtration rate (eGFR) of ≥30 mL/min per 1.73 m² of body surface area, and (4) a history of HF hospitalization within 12 months before enrollment or an elevated level of natriuretic peptide within 60 days before randomization (a BNP of ≥100 pg/mL or NT-proBNP (N-terminal pro-B-type natriuretic peptide) of ≥360 pg/mL). BNP or NT-proBNP was locally collected and processed as previously described.[18,19] This trial duration was ≈6 years (August 10, 2006–January 31, 2012), with an average subject follow-up of 3.3 years. TOPCAT complied with the Declaration of Helsinki and received ethical clearance. The study was approved by the institutional review board at each participating site. All patients signed informed consent before randomization. The primary results of the TOPCAT trial are published elsewhere.[18,19]

Follow-Up and End Point Definition

Patients were followed up for outcomes every 4 months during the study randomized in the first year and every 6 months thereafter. Stroke was defined as: (1) a focal neurologic deficit (resulting from a vascular cause involving the central nervous system) of sudden onset

that is not reversible within 24 hours (including death) and not because of other readily identifiable causes (eg, brain tumor, trauma), or (2) a focal neurologic deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that is reversible within 24 hours and brain imaging documenting a new infarction or hemorrhage (eg, magnetic resonance imaging with diffusion-weighted imaging). All stroke events were adjudicated by a clinical end point committee at Brigham and Women's Hospital, Boston, Massachusetts, according to prespecified criteria.[18]

Statistical Analysis

SPSS Statistics version 25.0 (IBM, Armonk, NY) and R version 4.0.3 software for Windows (R Foundation for Statistical Computing, Vienna, Austria) were used. The continuous variables are expressed as the mean with SD for the normally distributed data or median with interquartile range for the nonnormally distributed data. The normality of the data was analyzed using the Shapiro-Wilk test. The differences between the groups in the continuous variables were compared using unpaired Student t tests (normal distribution) or Mann-Whitney U tests (nonnormal distributions). The categorical variables, which are reported as count and percentage, were compared using χ^2 tests. The best cutoff value of BNP for predicting a stroke event during follow-up was explored by using regression tree analysis. Kaplan-Meier analysis with log-rank test was used for initial comparisons of stroke event among BNP groups. Proportionality assumption was assessed by plotting log minus log survival function. The Cox proportional hazard model calculated the adjusted hazard ratio (HR), and 95% CI of BNP associated with stroke risk was calculated. The adjusted variables were selected by stepwise methods ($P<0.1$) from all baseline factors and considering meaningful clinical variables. Furthermore, a Cox proportional hazard analysis with propensity score was performed using 1:1 nearest-neighbor matching without replacement to match significant baselines characteristics among BNP groups. The propensity score was derived using a logistic regression model that included BNP>278 pg/mL as the outcome variable and confounders with significant difference BNP groups, including age, sex, body mass index, ejection fraction, eGFR, history of AF, administration of diuretics, and β-blockers as explanatory variables. Standardized differences of <0.10 between propensity score–matched patients were considered negligible.

C index at 5 years in a crude Cox model was used to evaluate improvements of prognostic value by adding BNP to existing stroke risk models (CHADS$_2$, CHA$_2$DS$_2$-Vasc, R$_2$CHADS$_2$ scores). The calculation of these risk scores has been described previously.[20]

The C index of a BNP-added risk-predicting model versus existing risk-predicting model was compared by using the method of Delong et al.[21] The continuous net reclassification improvement (NRI) index and integrated discrimination improvement (IDI) index examined the improvement. CIs of C index, NRI scores, and IDI scores were computed by bootstrap resampling. $P<0.05$ was considered statistically significant in all analyses.

RESULTS

Characteristics of HFpEF Patients With or Without Baseline BNP Value

In total, 3445 subjects were recruited for the TOPCAT study; a total of 802 patients had baseline BNP values available, 799 of whom were included in our study after excluding individuals with missing covariates. There was a significant difference across the key characteristics of patients with HFpEF with or without baseline BNP value including age, race, and history of smoking (Table S1). In patients with available BNP levels, median (interquartile range) values were 71.0 years (64.0–79.0 years) for age, 31.2 kg/m^2 (26.7–38.3 kg/m^2) for body mass index, 63.1 mL/min per 1.73 m^2 (50.2–76.7 L/min per 1.73 m^2) for eGFR, and 61.8% had a history of AF. BNP ranged from 4 to 4943 pg/mL (median, 247 pg/mL; interquartile range, 143–443 pg/mL).

Characteristics of HFpEF Patients With or Without a Stroke Event After Randomization

Among 799 included subjects, there were 34 stroke events (1.52 per 100 patient-years) after a mean of 2.85 years of follow-up among 2238.51 patient-years. As shown in Table 1, the stroke group had a higher prevalence of AF, higher BNP levels, and more warfarin administration than the nonstroke group. There were no significant differences among age, sex, country, body mass index, New York Heart Association functional class, or other comorbidities between the 2 groups. Only a small proportion of the enrolled patients had baseline echocardiography data, which are summarized in Table S2. The patients who experienced stroke events had higher left ventricular relative wall thickness, higher posterior wall thickness, and higher right ventricular outflow tract velocity time integral.

Baseline BNP Levels and Associated Risk of Stroke

Regression tree analysis revealed the cutoff point of BNP at 278 pg/mL in predicting stroke. This cutoff point was evaluated by Kaplan-Meier analysis, which

Table 1.   Basic Characteristics of Stroke and Nonstroke Group

Variables	Nonstroke, n=765	Stroke, n=34	*P* value
Random to spironolactone	390 (48.8)	17 (50.0)	0.911
Demographics			
Age, y	71.0 (63.0, 79.0)	74.0 (67.8, 81.3)	0.067
Sex, men, n (%)	387 (48.4)	23 (67.6)	0.052
Race, White, n (%)	607 (76.0)	28 (82.4)	0.671
Country, United States, n (%)	565 (70.7)	27 (79.4)	0.469
BMI, kg/m^2	32.4 (27.8, 37.8)	31.2 (26.7, 38.3)	0.436
Smoking history	411 (51.4)	23 (67.6)	0.111
Alcohol drinking, n (%)			0.327
0	573 (71.7)	28 (82.4)	
1–5 drinks per wk	132 (16.5)	4 (11.8)	
6–10 drinks per wk	43 (5.4)	2 (5.9)	
10+ drinks per wk	17 (2.1)	0 (0)	
Physical examination			
EF, %	58.0 (53.0, 63.0)	59.5 (55.0, 62.3)	0.817
NYHA, class III–IV, n (%)	288 (36.0)	13 (38.2)	0.945
Heart rate, bpm	68.0 (60.0, 76.0)	69.5 (60.0, 78.0)	0.760
SBP, mmHg	129.0 (118.0, 138.0)	130.0 (122.0, 145.0)	0.067
DBP, mmHg	70.0 (62.0, 80.0)	74.0 (65.5, 83.3)	0.110
eGFR, mL/min per 1.73 m^2	63.3 (50.2, 77.1)	61.3 (48.3, 72.1)	0.253
BNP, pg/mL	241.0 (142.0, 439.5)	375.0 (213.8, 610.3)	0.006
Comorbidities, n (%)			
Previous hospitalization for CHF	344 (43.1)	17 (50)	0.564
Previous MI	178 (22.3)	12 (35.3)	0.107
Previous stroke	81 (10.1)	3 (8.8)	0.966
Previous CABG	142 (17.8)	8 (23.5)	0.468
Previous PCI	169 (21.2)	11 (32.4)	0.161
COPD	123 (15.4)	6 (17.6)	0.808
Hypertension	693 (86.7)	33 (97.1)	0.328
Peripheral artery disease	88 (11.0)	6 (17.6)	0.415
Dyslipidemia	561 (70.2)	28 (82.4)	0.242
AF	309 (38.7)	21 (61.8)	0.013
Diabetes	320 (40.1)	16 (47.1)	0.546
Medications, n (%)			
Diuretic	651 (81.5)	29 (85.3)	0.975
ACEI	379 (47.4)	20 (58.8)	0.290
ARB	217 (27.2)	8 (23.5)	0.540
β-blocker	619 (77.5)	28 (82.4)	0.834
Calcium channel blocker	306 (38.3)	13 (38.2)	0.837
Aspirin	475 (59.4)	24 (70.6)	0.317
Statin	491 (61.5)	26 (76.5)	0.142
Warfarin	245 (30.7)	17 (50.0)	0.029
Scores			
CHADS$_2$	3 (2, 3)	3 (3, 3)	0.087
CHA$_2$DS$_2$-VASc	4 (4, 5)	5 (2, 5)	0.176
R$_2$CHADS$_2$	4 (3, 5)	3.5 (3, 5)	0.348

The continuous variables are expressed as the mean with SD for the normally distributed data or median with interquartile range for the nonnormally distributed data. ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure.

showed that patients with BNP>278 pg/mL experienced a higher risk of stroke (P<0.001) (Figure 1). The basic characteristics of subjects stratified by baseline BNP level are presented in Table S3. The patients in the lower BNP group (BNP≤278 pg/mL) were younger, more likely to be women, had higher body mass index, ejection fraction, and eGFR, and had lower prevalence of AF and diuretic administration, and lower β-blocker administration than the higher BNP group (BNP>278 pg/mL). Baseline echocardiography with a small proportion of the enrolled patients is presented in Table S4.

The results of Cox regression showed that BNP levels >278 pg/mL were associated with an increased risk of stroke after adjusting for age, sex, previous stroke, diabetes, previous myocardial infarction, AF, smoking, spironolactone use, New York Heart Association class, warfarin, aspirin, and eGFR (hazard ratio [HR], 3.24 [95% CI, 1.49–7.06]) (Table 2).

Discriminatory Capacity of Adding BNP to Existing Stroke Risk Scores

The discriminatory performances of BNP for predicting stroke in patients with HFpEF were expressed as the C index. A BNP level of >278 pg/mL showed a moderate performance for 5-year stroke prediction (C index, 0.67 [95% CI, 0.60–0.74]), with a sensitivity of 0.81 and specificity of 0.56 (Table 3).

We assessed the predictive ability of BNP by adding a BNP level of >278 pg/mL as an additional parameter to existing stroke risk scores, including $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores. In regard to 5-year stroke risk, the addition of BNP to existing stroke risk scores significantly improved the discrimination assessed by C index, NRI, and IDI compared with that of the risk scores alone ($CHADS_2$: C index, 0.67; BNP+$CHADS_2$: C index, 0.77, P=0.004; NRI, 40.9%; IDI, 3.0%; CHA_2DS_2-VASc: C index, 0.64; BNP+CHA_2DS_2-VASc: C index, 0.74, P=0.050; NRI, 41.4%; IDI, 2.2%; R_2CHADS_2: C index, 0.70; BNP+R_2CHADS_2: C index, 0.78, P=0.029; NRI, 40.9%; IDI, 3.2%) (Table 3, Figure 2).

Sensitivity Analysis

We performed a sensitivity analysis after excluding individuals from Russia/Georgia because of the regional variation in patients and outcomes in the TOPCAT trial. The results confirmed better discrimination of existing BNP-added risk scores assessed by C index and the

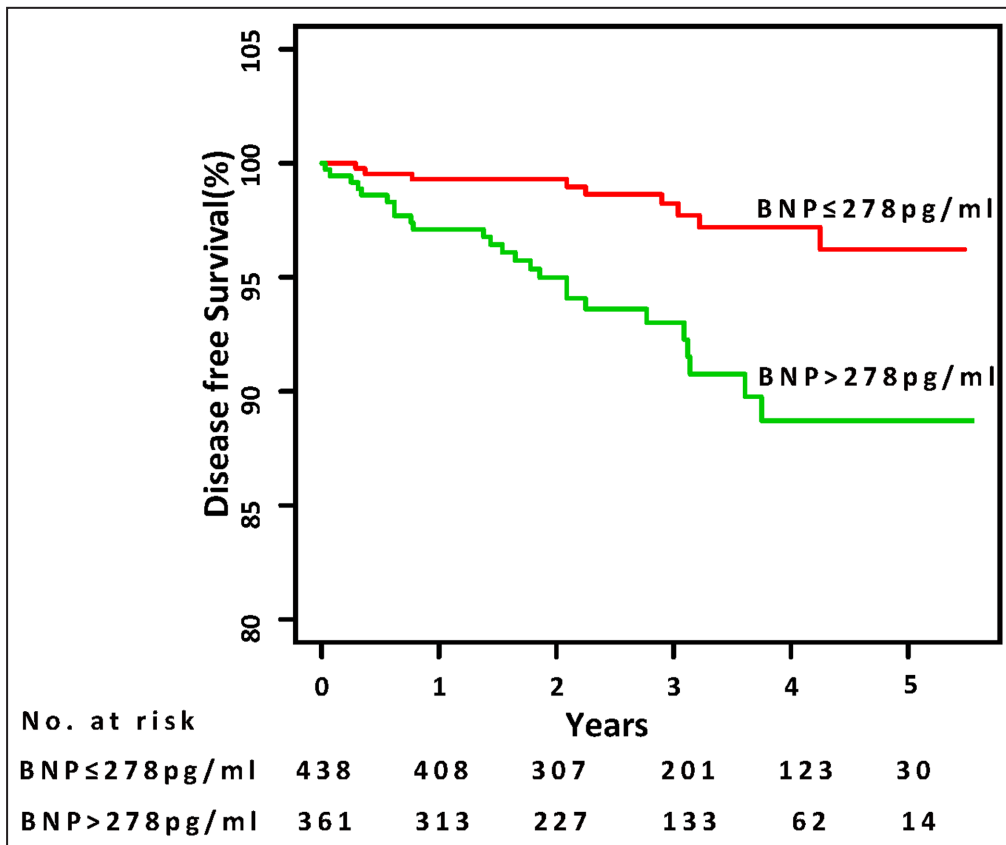| No. at risk						
	0	1	2	3	4	5
BNP≤278pg/ml	438	408	307	201	123	30
BNP>278pg/ml	361	313	227	133	62	14

Figure 1.   Kaplan-Meier analysis for stroke in high BNP>278 pg/mL and low BNP (BNP≤278 pg/mL) groups.
Stroke-free survival was analyzed by a log-rank test (P<0.001). BNP indicates B-type natriuretic peptide.

Table 2. Univariate and Multivariate Cox Regression Analysis of BNP Groups With Outcome of Stroke

Sensitivity analyses	Cases (%)	Person-years	Incidence rate, per 100 person-years	Unadjusted HR (95% CI), *P* value	Adjusted HR (95% CI), *P* value
All included patients,* n=799	34 (4.26)	2238.51	1.52		
BNP≤278 pg/mL, n=438	9 (2.05)	1304.94	0.69	Ref	Ref
BNP>278 pg/mL, n=361	25 (6.93)	933.57	2.68	3.88 (1.81–8.31), 0.001¶	3.24 (1.49–7.06), 0.003¶
Excluding patients with AF,† n=469	13 (2.77)	1333.52	0.97		
BNP≤278 pg/mL, n=278	4 (1.44)	829.49	0.48	Ref	Ref
BNP>278 pg/mL, n=191	9 (4.71)	441.03	2.04	3.64 (1.12–11.82), 0.032¶	3.42 (1.02–11.48), 0.047¶
Excluding patients from Russia/Georgia,‡ n=695	31 (4.46)	1987.47	1.56		
BNP≤278 pg/mL, n=373	8	1144.51	0.70	Ref	Ref
BNP>278 pg/mL, n=322	23	842.96	2.73	3.93 (1.76–8.79), 0.001¶	3.28 (1.44–7.47), 0.005¶
Excluding patients treated with warfarin,§ n=537	17 (3.17)	1489.30	1.14		
BNP≤278 pg/mL, n=305	5	908.05	0.55	Ref	Ref
BNP>278 pg/mL, n=232	12	581.25	2.06	3.67 (1.29–10.44), 0.015¶	3.42 (1.16–10.13), 0.026¶
Propensity score matched‖					
BNP≤278 pg/mL, n=305	6	929.21	0.65	Ref	Ref
BNP>278 pg/mL, n=232	22	808.03	2.72	4.17 (1.69–10.29), 0.002¶	4.12 (1.66–10.24), 0.002¶

P≤0.05 is statistically significant. AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; HR, hazard ratio; and Ref, reference.

*HR adjusted for age, sex, previous stroke, diabetes, previous myocardial infarction, AF, smoking, spironolactone using, New York Heart Association function class, warfarin, aspirin, estimated glomerular filtration rate.

†HR adjusted for previous myocardial infarction, age, sex, previous stroke, diabetes, smoking, spironolactone using, New York Heart Association function class, warfarin, aspirin, estimated glomerular filtration rate.

‡HR adjusted for age, sex, previous stroke, diabetes, previous myocardial infarction, AF, smoking, spironolactone using, New York Heart Association function class, warfarin, aspirin, estimated glomerular filtration rate.

§HR adjusted for age, sex, previous stroke, diabetes, previous myocardial infarction, AF, smoking, spironolactone using, New York Heart Association function class, aspirin, estimated glomerular filtration rate.

‖HR variables including age, sex, body mass index, ejection fraction, estimated glomerular filtration rate, history of AF; administration of diuretic and β-blocker was included in the propensity score. Adjusted for previous stroke, diabetes, previous myocardial infarction, smoking, spironolactone, New York Heart Association function class, warfarin, aspirin.

¶*P*<0.05.

corresponding NRI and IDI values (Table S5). Sensitivity analysis performed by excluding patients treated with warfarin or those with AF showed similar results (Table S5). Sensitivity analyses by competing Cox generated confirmed results, with elevated BNP levels for stroke (HR, 3.77 [95% CI, 1.72–8.29]; *P*=0.001).

An additional sensitivity analysis using propensity score matching was further developed to verify the association between BNP and the risk of stroke in patients with HFpEF. A total of 626 individuals from 799 patients were identified, of which 313 were in each BNP group. The basic characteristics did not significantly differ among BNP groups after matching (Table S6). The risk of stroke was significantly higher in propensity score–matched patients with BNP levels >278 pg/mL (HR, 4.12 [95% CI, 1.66–10.24]) (Table 2).

DISCUSSION

Based on a secondary analysis from the TOPCAT trial, we showed that (1) high BNP was associated with an increased risk of stroke in patients with HFpEF;

(2) addition of BNP to $CHADS_2$/CHA_2DS_2-VASc/R_2CHADS_2 scores significantly improved the discrimination for stroke prediction in HFpEF; and (3) sensitivity analyses by excluding patients with AF at baseline, those in Russia/Georgia, and those being treated with warfarin generated confirmatory results. Overall, our findings first suggest that BNP could predict the risk of stroke in patients with HFpEF.

Stroke is one of the devastating adverse events in HF and contributes to high mortality and morbidity. As the common cause of stroke among patients with HF, AF has been studied for several decades.[22] However, pooled analysis of Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved and Irbesartan in Heart Failure With Preserved Systolic Function trials showed that in patients with HFpEF without AF, the stroke incidence (1.0% per year) was similar to the rate in HF with reduced ejection fraction without AF (1.2% per year).[4] Moreover, Cogswell et al found a high prevalence of subclinical cerebral infarcts in the HFpEF population with no prior AF diagnosis compared with those with AF (29.3% versus 23.5%, respectively).[23] Catheter ablation of AF in a

Table 3. C Index, NRI, and IDI for Evaluating Improvement to Predict Stroke After Adding BNP to Scores of CHADS$_2$, CHA$_2$DS$_2$-VASc, and R$_2$CHADS$_2$, in Patients With Heart Failure With Preserved Ejection Fraction

Clinical model	C index (95% CI)	Sensitivity, specificity	Clinical model+BNP			Clinical model vs clinical model+BNP			
			P value for C index	C index (95% CI)	Sensitivity, specificity	NRI % (95% CI)	P value for NRI	IDI % (95% CI)	P value for IDI
BNP	0.67 (0.60–0.74)	0.81, 0.56							
CHADS$_2$	0.67 (0.61–0.73)	0.77, 0.51	0.004	0.77 (0.70–0.84)	0.73, 0.73	40.9 (19.0–53.8)	<0.0001	3.0 (0.8–6.8)	<0.0001
CHA$_2$DS$_2$-VASc	0.64 (0.55–0.72)	0.79, 0.43	0.050	0.74 (0.67–0.81)	0.75, 0.67	41.4 (22.7–56.0)	<0.0001	2.2 (0.7–7.0)	<0.0001
R$_2$CHADS$_2$	0.70 (0.63–0.78)	0.85, 0.41	0.029	0.78 (0.71–0.86)	0.80, 0.65	40.9 (22.2–55.4)	<0.0001	3.20 (0.9–8.3)	<0.0001

BNP indicates B-type natriuretic peptide; IDI, integrated discrimination improvement; and NRI, net reclassification improvement.

randomized controlled clinical trial also failed to reduce the risk of stroke.[10] Overall, AF cannot directly explain stroke risk in HFpEF, and HFpEF itself might be a substrate for stroke incidents.[10] Recent studies have suggested the development of left atrial (LA) myopathy (as reflected by LA geometry, LA mechanical function, or LA fibrosis) is central to the pathogenesis of HFpEF.[10] Furthermore, accumulating evidence showed LA myopathy was a direct causal mechanism contributing to thromboembolic stroke independent of the presence or control of AF.[24,25] Our results supported this hypothesis. A prospective study by Patel et al[26] showed LA myopathy, indicated by LA reservoir strain abnormality, was associated with decreased stroke volume and poor left ventricle diastolic function, independently of AF status, and eventually contributed to elevated BNP. Therefore, BNP levels might be an indicator for LA myopathy, even in HFpEF without AF, and thus might be an early biomarker that can predict stroke, regardless of AF.

Several risk tools were tested for their predictive ability for stroke in patients with AF. We previously showed that CHA$_2$DS$_2$-VASc (C statistic, 0.62) scores did not achieve an excellent predictive ability for stroke, regardless of AF status.[9,20] Abdul-Rahim and coworkers developed a complicated model for stroke in patients with HFpEF without AF, with a higher performance from the CHARM-Preserved (C statistic, 0.71) and I-Preserve (C statistic, 0.73) trials; furthermore, the model worked exceptionally well with an external validation cohort of TOPCAT (C statistic, 0.73).[4] These results suggested the generality of risk scores across different baseline characteristics across the population. Notably, none of their models included the BNP level.[4] Our results showed that the predictive ability of BNP significantly improved the predictive power of established stroke risk scores, even in the absence of AF. However, our results should be considered exploratory and should be validated in more populations with HFpEF, especially in patients without AF.

In patients with AF, NT-proBNP is independently associated with an increased risk of stroke. Our sensitivity analysis showed that among those with HFpEF without AF history, the addition of BNP to existing stroke risk scores still significantly improved the C statistic, which suggested BNP's predictive ability for stroke in HFpEF independent of AF history. Nevertheless, we should also point out that the comorbidities analyzed in our study were restricted to baseline characteristics, and the occurrence of AF during the follow-up might have also largely contributed to the incidence of stroke; therefore, whether BNP predicts stroke independently of AF needs to be further validated. On the other hand, circulating BNP levels are largely influenced by renal function.[27,28] Therefore, we adjusted the Cox
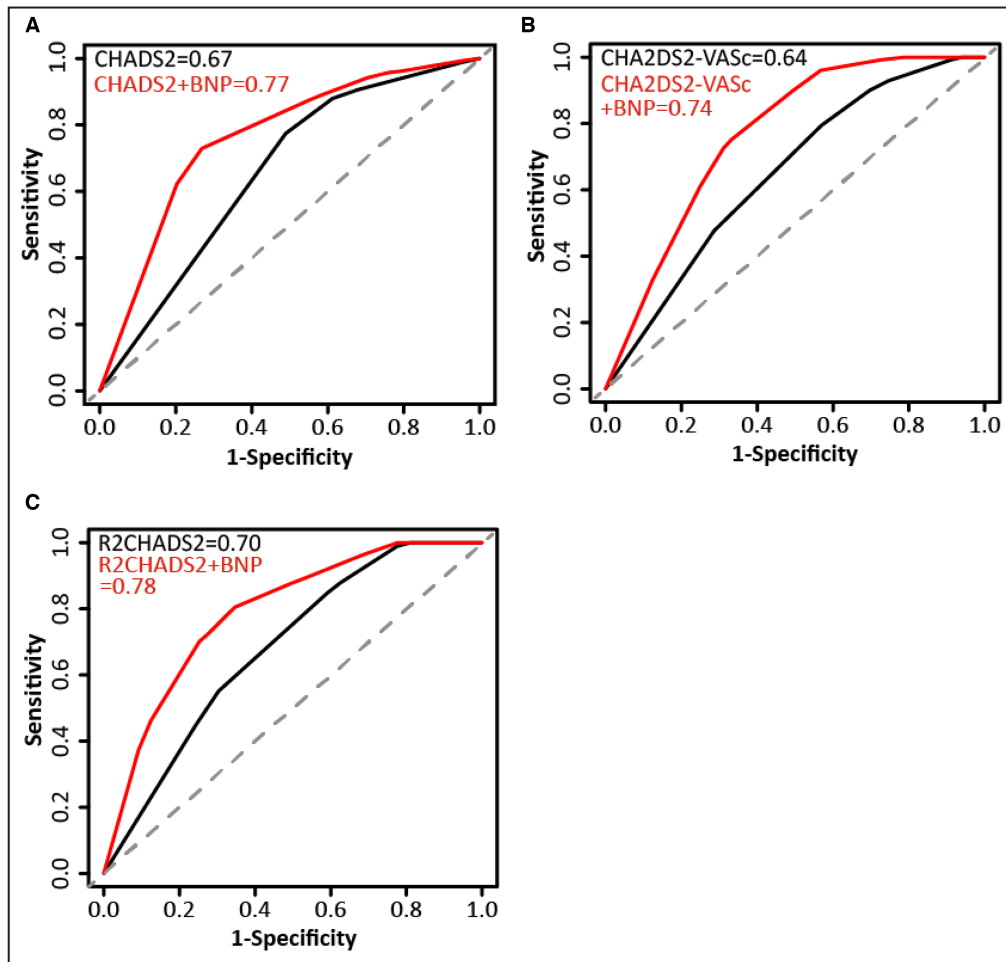
Figure 2. Receiver operating characteristic curves of CHADS$_2$/CHA$_2$DS$_2$-VASc/R$_2$CHADS$_2$ score and BNP-added CHADS$_2$/CHA$_2$DS$_2$-VASc/R$_2$CHADS$_2$ score for predicting stroke.

The BNP-added CHADS$_2$/CHA$_2$DS$_2$-VASc/R$_2$CHADS$_2$ score was compared with CHADS$_2$/CHA$_2$DS$_2$-VASc/R$_2$CHADS$_2$ score for predicting future stroke by using the C index. The CHADS$_2$,CHA$_2$DS$_2$-VASc,R$_2$CHADS$_2$scores are simple clinical scores which were employed to stratify the risk of systemic thromboembolic complications in patients with atrial fibrillation. Sensitivity indicates the ability of a test to correctly identify patients with a disease. Specificity indicates the ability of a test to correctly identify people without the disease. BNP indicates B-type natriuretic peptide.

regression for eGFR, and the result is still significant. Although our result showed a statistically significant association between BNP and the risk of stroke, the predictive ability of BNP in patients with HFpEF with and without kidney dysfunction should also be evaluated in future research.

Besides cardiomyocytes, BNP also could be released from the hypothalamus in response to acute cerebral ischemia.[29,30] However, the TOPCAT trial excluded patients with stroke in the past 90 days[18]; thus, the increased BNP level secreted from the hypothalamus was limited in our present study.

The most recent HF guidelines stated that anticoagulation should be considered for patients with HF and AF, if eligible, as assessed by the CHA$_2$DS$_2$-VASc score. However, they did specify types of HF.

Therefore, although CHA$_2$DS$_2$-VASc is mainly based on HF with reduced ejection fraction, and criteria for anticoagulation for AF and HFpEF are in reality lacking, we fully agree with the opinion raised by Mulder et al that anticoagulation must be seriously considered in many patients with AF and HFpEF.[31] The benefit of anticoagulation therapy based on BNP's addition to CHA$_2$DS$_2$-VASc in HFpEF and AF may be further studied. For HF without AF, a recent Cochrane systematic review by Lip et al does not support the routine use of oral anticoagulation therapy in patients with chronic HF with no AF because of the benefit-to-risk imbalance.[32] Therefore, it is still uncertain whether patients with HFpEF in sinus rhythm are at a particularly high risk of stroke benefit from the use of anticoagulants. New risk scores, such as combined BNP and other clinical risk

factors, are needed to guide the use of anticoagulation therapy in HF without AF.

Interestingly, NT-proBNP was one of the components of the ABC (age, biomarkers, clinical history) stroke risk score, a biomarker-based risk score for predicting stroke in AF, which somewhat supports our finding. In addition to BNP, other biomarkers, such as inflammation and fibrotic myopathy, have also been considered effective predictors of stroke.[33] For example, plasma high-sensitivity cardiac troponin levels, another component of the ABC risk score, has also been validated as a component for predicting stroke. Plasma high-sensitivity cardiac troponin levels are a well-reported prognostic marker in patients with cardiovascular diseases, including HFpEF.[34,35] However, there are limited studies examining the predictive ability of plasma high-sensitivity cardiac troponin levels and stroke in patients with HFpEF, which might be studied in subsequent research.

Strengths and Limitations

Our study has several strengths. To our knowledge, this was the first study to evaluate the performance of BNP to predict the occurrence of stroke in patients with HFpEF.

Nevertheless, several limitations should be acknowledged. First, this is a post hoc analysis based on the TOPCAT data set, and measured and unmeasured covariates might have potentially influenced the results. Second, the specified subtypes of stroke, such as ischemic stroke and embolic stroke, were not analyzed in the study because of the limited number of stroke events. Third, a history of transient ischemic attack and thromboembolic events was not available in the TOPCAT; thus, whether the predictive ability of BNP is independent of a history of transient ischemic attack and thromboembolic events remains unclear. Fourth, because of availability of BNP values, our analysis was restricted to a minority of TOPCAT participants, and there was a significant difference between some characteristics of included and excluded participants. However, the average incidence rate of stroke was 1.5 per 100 patient-years in the present study, which is similar to the patients with HFpEF in the overall TOPCAT trial and the CHARM-Preserved and I-Preserve trials. Thus, our cohort may be representative of general HFpEF in the association between BNP and stroke. Fifth, NT-proBNP was not examined because of data restrictions (limited stroke cases). A previous meta-analysis showed a comparable diagnostic performance between BNP and NT-proBNP for cardioembolic stroke[36]; however, the predictive ability of NT-proBNP for stroke should be studied in future studies.

CONCLUSIONS

BNP is associated with an increased risk of stroke in patients with HFpEF and may be a valuable biomarker for stroke prediction in patients with HFpEF. However, our findings need to be further confirmed, and the specific threshold should be prospectively reexamined.

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SUPPLEMENTAL MATERIAL

Table S1. Basic characteristics of patients with Heart Failure with Preserved Ejection Fraction stratified by missed or documented BNP groups

Variables	Missed BNP (n=2646)	Documented BNP (n=799)	*P*-value
Random to spironolactone, n (%)	1315 (49.7)	407 (50.9)	0.566
Demographics			
Age, years	68.00 (60.0, 75.0)	71.00 (64.0, 79.0)	**<0.001**
Sex, male, n (%)	1260 (47.6)	410 (51.3)	0.073
Race, white, n (%)	2427 (91.7)	635 (79.5)	**<0.001**
BMI, kg/m^2	30.59 (27.10, 35.0)	32.14 (27.73, 37.8)	**<0.001**
Smoking history, n (%)	1195 (45.2)	433 (54.2)	**<0.001**
Alcohol drinking drinks/week, n (%)			
0	2086 (78.8)	601 (75.2)	**0.002**
1-5	444 (16.8)	136 (17.0)	
6-10	81 (3.1)	45 (5.6)	
10+	35 (1.3)	17 (2.1)	
Physical examination			
EF, %	56.0 (51.0, 61.0)	58.0 (53.50, 63.0)	**<0.001**
NYHA(III-IV), n (%)	835 (31.6)	301 (37.7)	**0.001**
Heart rate, bpm	68.0 (62.0, 76.0)	68.0 (60.0, 76.0)	0.135
SBP, mmHg	130.0 (120.0, 140.0)	129.0 (118.0, 138.0)	**0.001**
DBP, mmHg	80.0 (70.0, 82.0)	70.0 (62.0, 80.0)	**<0.001**
eGFR, ml/min*1.73m^2	66.0 (54.92, 79.52)	63.1 (50.2, 76.7)	**<0.001**
Comorbidities, n (%)			
Pervious	2131 (80.5)	361 (45.2)	**<0.001**

hospitalization for CHF			
Pervious MI	703 (26.6)	190 (23.8)	0.126
Pervious stroke	181 (6.8)	84 (10.5)	**0.001**
Pervious CABG	293 (11.1)	150 (18.8)	**<0.001**
Pervious PCI	320 (12.1)	180 (22.5)	**<0.001**
COPD	274 (10.4)	129 (16.1)	**<0.001**
Hypertension	2424 (91.6)	726 (90.9)	0.556
Peripheral artery disease	225 (8.5)	94 (11.8)	**0.007**
Dyslipidemia	884 (33.4)	330 (41.3)	**<0.001**
AF			
Diabetes	782 (29.6)	336 (42.1)	**<0.001**
Medications, n (%)			
Diuretic	2137 (80.8)	680 (85.1)	**0.006**
ACEI	1853 (70.0)	399 (49.9)	**<0.001**
ARB	473 (17.9)	225 (28.2)	**<0.001**
Beta blocker	2029 (76.7)	647 (81.0)	**0.012**
Calcium channel blocker	975 (36.8)	319 (39.9)	0.125
Aspirin	1751 (66.2)	499 (62.5)	0.058
Statin	1288 (48.7)	517 (64.7)	**<0.001**
Warfarin	525 (19.8)	262 (32.8)	**<0.001**

BMI: body mass index, EF: ejection fraction, NYHA: New York heart function class, bpm: beat per minutes, SBP: systolic blood pressure, DBP: diastolic blood pressure, GFR: estimated glomerular filtration rate, BNP: B-type natriuretic peptide, CHF: chronic heart failure, ,MI: myocardial infarction, CABG: coronary artery bypass grafting ,PCI: Percutaneous coronary intervention, COPD: chronic obstructive pulmonary disease, AF: Atrial fibrillation, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker.

Table S2. Baseline echocardiographic characteristics of Heart Failure with Preserved Ejection Fraction patients stratified by stroke post randomization

Variables	Non-stroke	Stroke	*P*-value
Eccentric mitral regurgitation (n=232)	4 (1.8%)	1 (14.3%)	0.143
Moderate or greater mitral regurgitation (n=232)	36 (16.0%)	1 (14.3%)	1.000
Interventricular septum thickness (n=315)	1.19 (1.05, 1.32)	1.26 (1.16, 1.39)	0.903
Posterior wall thickness (n=315)	1.13 (1.02, 1.27)	1.23 (1.15, 1.43)	0.048
End-diastolic left ventricular diameter (n=315)	4.83±0.60	4.71±0.53	0.520
Maximal left atrial anterior-posterior diameter (n=315)	4.33 (3.98, 4.80)	4.15 (3.95, 4.80)	0.772
Peak E wave velocity (n=284)	92.78±30.36	106.81±35.91	0.176
Peak A wave velocity (n=209)	74.24±25.61	66.48±28.62	0.505
Lateral early diastolic myocardial velocity (n=200)	7.47 (5.81, 9.91)	8.30 (7.67, 9.42)	0.235
Lateral late diastolic myocardial velocity (n=157)	8.20 (5.82, 10.28)	6.09 (3.87, 16.90)	0.445
Mitral regurgitation jet area (n=247)	0.95 (0.00, 2.78)	0.00 (0.00, 2.04)	0.327
E wave deceleration time (n=282)	193.33 (156.67, 236.67)	203.33 (195.00, 223.33)	0.394
Peak tricuspid regurgitation velocity (n=197)	271.91 (244.63, 306.89)	236.73 (211.50, 305.39)	0.113
E/A ratio (n=208)	1.12 (0.82, 1.57)	1.75 (0.75, 3.40)	0.294
End-systolic left ventricular diameter (n=315)	3.36 (3.00, 3.69)	3.27 (2.94, 3.58)	0.489
Septal early diastolic myocardial velocity(n=223)	5.67 (4.53, 7.24)	6.95 (6.12, 8.17)	0.059
Septal late diastolic myocardial velocity (n=162)	7.03 (5.15, 8.45)	4.74 (4.53, -)	0.071
RV end diastolic area (n=237)	19.78 (16.03, 24.03)	17.64 (17.01, 21.29)	0.563
RV end systolic area (n=237)	9.76 (7.72, 12.89)	8.77 (8.01, 11.78)	0.651
Lateral systolic myocardial velocity (n=199)	6.44 (5.45, 7.58)	6.15 (4.88, 8.70)	0.707
Septal systolic myocardial velocity (n=222)	5.65 (4.82, 6.69)	5.40 (4.57, 6.11)	0.509

Left atrial area (n=286)	19.55 (16.48, 23.51)	22.13 (18.98, 24.05)	0.233
Mean LV wall thickness (n=315)	1.16 (1.03, 1.28)	1.26 (1.15, 1.43)	0.061
Lv mass (n=315)	210.87 (167.28, 270.55)	210.66 (195.87, 266.71)	0.564
Ejection Fraction (n=319)	59.89 (55.98, 65.18)	57.54 (56.18, 66.55)	0.618
E/Em septal ratio (n=217)	15.30 (11.97, 19.78)	16.82 (13.66, 18.74)	0.797
RV fractional area change (n=237)	0.50 (0.43, 0.54)	0.48 (0.44, 0.54)	0.981
E/Em lateral ratio (n=195)	10.94 (8.29, 15.46)	13.22 (8.48, 16.70)	0.692
Simpson Ejection fraction (n=298)	60.46 (56.34, 65.35)	58.34 (56.46, 66.59)	0.992
Teicholtz end-diastolic volume (n=315)	110.50 (88.92, 129.87)	105.96 (73.08, 126.07)	0.526
Teicholtz end-systolic volume (n=315)	46.27 (35.04, 57.69)	43.06 (33.40, 53.70)	0.489
Teicholtz Ejection fraction (n=315)	58.01 (53.19, 60.97)	59.44 (55.23, 60.94)	0.583
End-diastolic volume (n=298)	96.08 (72.87, 120.72)	96.32 (88.19, 134.08)	0.290
End-systolic volume (n=298)	37.00 (25.84, 48.36)	40.13 (34.97, 50.14)	0.357
LA volume (n=293)	57.15 (45.59, 74.84)	67.96 (56.11, 73.07)	0.306
LV relative wall thickness (n=315)	0.47 (0.42, 0.53)	0.51 (0.49, 0.57)	0.015
MR jet area-to-left atrial area ratio (n=232)	0.05 (0.00, 0.13)	0.00 (0.00, 0.10)	0.445
Stroke volume (n=298)	57.28 (44.88, 71.32)	63.09 (49.62, 86.63)	0.259
Abnormal E' (n=248)	170 (71.1%)	5 (55.6%)	0.526
Diastolic dysfunction grade (n=209)	1.00 (0.00, 2.00)	0.00 (0.00. 2.25)	0.327
Diastolic dysfunction grade (modified Olmsted criteria) (n=167)	2.00 (1.00, 2.00)	2.50 (1.25, 3.00)	0.374
Longitudinal Strain (n=205)	-15.49±3.49	-14.80±1.43	0.693
Abnormal Longitudinal Strain (n=205)	105 (52.2%)	3 (75.0%)	0.691
Quartile of Longitudinal Strain (n=205)	3.00 (1.00, 4.00)	2.50 (2.00, 3.75)	0.692
Moderate or greater aortic stenosis (n=259)	3 (1.2%)	0 (0.0%)	1.000
Moderate aortic regurgitation (n=306)	5 (1.7%)	0 (0.0%)	1.000

Prosthetic valve (n=319)	13 (4.2%)	1 (9.1%)	0.395
Was color doppler missing in study (n=319)	12 (3.9%)	0 (0.0%)	1.000
AV peak velocity (n=259)	139.23 (116.30, 173.48)	140.09 (120.97, 164.89)	0.931
Right ventricular outflow tract velocity time integral (n=189)	16.59 (13.88, 19.67)	21.92 (16.71, 23.88)	0.050
Abnormal relative wall thickness(n=315)	230 (75.7%)	11 (100%)	0.131
Pulmonary vascular resistance (n=148)	1.80 (1.57, 2.21)	1.64 (1.14, 1.99)	0.183
Significant valvular disease (n=309)	51 (17.1%)	2 (18.2%)	1.000

E = Early wave of mitral inflow, E'= early diastolic mitral annular velocity, LV= Left ventricle, ESV= end systolic volume, EDV= end diastolic volume.

Table S3. Basic characteristics of patients with Heart Failure with Preserved Ejection Fraction stratified by BNP groups

Variables	BNP≤278 pg/mL (n=438)	BNP >278 pg/mL (n=361)	*P*-value
Random to spironolactone	217 (49.5)	190 (52.6)	0.385
Demographics			
Age, years	70.0 (62.0, 78.0)	73.0 (65.0, 81.0)	**<0.001**
Sex, male	209 (47.7)	201 (55.7)	**0.025**
Race, white	345 (78.8)	290 (80.3)	0.586
BMI, kg/m^2	33.1 (28.3, 38.6)	31.18 (26.4, 37.2)	**0.004**
Smoking history	228 (52.1)	206 (57.1)	0.157
Alcohol drinking drinks/week			0.791
0	328 (74.9)	273 (75.6)	
1-5	75 (17.1)	61 (16.9)	
6-10	25 (5.7)	20 (5.5)	
10+	10 (2.3)	7 (1.9)	
Physical examination			
EF, %	60.0 (55.0, 64.0)	55.0 (50.0, 61.0)	**0.001**
NYHA(III-IV)	170 (38.8)	131 (36.3)	0.464
Heart rate, bpm	67.0 (60.0,76.0)	69.0 (62.0, 76.0)	0.095
SBP, mmHg	128.0 (118.0, 138.0)	130.0 (118.0, 139.0)	0.779
DBP, mmHg	70.0 (64.0, 80.0)	70.0 (62.0, 80.0)	0.203
GFR, ml/min*1.73m^2	64.3 (51.5, 79.3)	61.2 (47.0, 74.8)	**0.005**
BNP, pg/ml	149.0 (116.0, 199.8)	483.0 (358.5, 720.5)	**<0.001**
Comorbidities, n (%)			

Pervious hospitalization for CHF	188 (42.9)	173 (47.9)	0.158
Pervious MI	107 (24.4)	83 (23.0)	0.635
Pervious stroke	47 (10.7)	37 (10.2)	0.825
Pervious CABG	74 (16.9)	76 (21.1)	0.134
Pervious PCI	92 (21.0)	88 (24.4)	0.256
COPD	72 (16.4)	57 (15.8)	0.804
Hypertension	397 (90.6)	329 (91.1)	0.808
Peripheral artery disease	48 (11.0)	46 (12.7)	0.436
Dyslipidemia	324 (74.0)	265 (73.4)	0.857
AF	160 (36.5)	170 (47.1)	**0.003**
Diabetes	171 (39.0)	165 (45.7)	0.058
Medications, n (%)			
Diuretic	355 (81.1)	325 (90.0)	**<0.001**
ACEI	209 (47.7)	190 (52.6)	0.167
ARB	124 (28.3)	101 (28.0)	0.917
Beta blocker	341 (77.9)	306 (84.8)	**0.013**
Calcium channel blocker	186 (42.5)	133 (36.8)	0.106
Aspirin	284 (64.8)	215 (59.6)	0.125
Statin	286 (65.3)	231 (64.0)	0.700
Warfarin	133 (30.4)	129 (35.7)	0.108
Scores			
CHADS2	3 (2-3)	3 (2-3)	**0.033**
CHA2DS2-VASc	4 (4-5)	5 (4-5)	0.181

R2CHADS2	4 (3-5)	4 (3-5)	**0.008**

BMI: body mass index, EF: ejection fraction, NYHA: New York heart function class, bpm: beat per minutes, SBP: systolic blood pressure, DBP: diastolic blood pressure, GFR: estimated glomerular filtration rate, BNP: B-type natriuretic peptide, CHF: chronic heart failure, ,MI: myocardial infarction, CABG: coronary artery bypass grafting ,PCI: Percutaneous coronary intervention, COPD: chronic obstructive pulmonary disease, AF: Atrial fibrillation, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker.

Table S4. Baseline echocardiographic characteristics of Heart Failure with Preserved Ejection Fraction patients stratified by BNP groups

Variables	BNP≤278 pg/mL	BNP >278 pg/mL	*P*-value
Eccentric mitral regurgitation (n=232)	0 (0.0%)	5 (4.4%)	0.062
Moderate or greater mitral regurgitation (n=232)	9 (7.6%)	28 (24.8%)	0.000
Interventricular septum thickness (n=315)	1.15 (1.04, 1.28)	1.23 (1.08, 1.35)	0.009
Posterior wall thickness (n=315)	1.11 (1.01, 1.25)	1.19 (1.03, 1.30)	0.011
End-diastolic left ventricular diameter (n=315)	4.83±0.57	4.81±0.62	0.827
Maximal left atrial anterior-posterior diameter (n=315)	4.22 (3.95, 4.66)	4.46 (4.03, 4.87)	0.004
Peak E wave velocity (n=284)	87.60±29.50	99.53±30.63	0.001
Peak A wave velocity (n=209)	74.89±23.78	72.85±28.18	0.585
Lateral early diastolic myocardial velocity (n=200)	7.57 (6.01, 9.64)	7.44 (5.66, 10.54)	0.906
Lateral late diastolic myocardial velocity (n=157)	8.51 (6.25, 10.57)	7.62 (5.03, 9.80)	0.056
Mitral regurgitation jet area (n=247)	0.71 (0.00, 1.93)	1.37 (0.00, 3.81)	0.003
E wave deceleration time (n=282)	195.00 (163.33, 240.83)	193.33 (140.00, 226.67)	0.070
Peak tricuspid regurgitation velocity (n=197)	261.88 (241.89, 296.08)	277.30 (248.43, 318.27)	0.039
E/A ratio (n=208)	1.03 (0.82, 1.40)	1.34 (0.83, 1.92)	0.017
End-systolic left ventricular diameter (n=315)	3.23 (2.99, 3.64)	3.41 (3.01, 3.72)	0.398
Septal early diastolic myocardial velocity(n=223)	5.66 (4.54, 7.37)	5.79 (4.49, 7.20)	0.982
Septal late diastolic myocardial velocity (n=162)	7.60 (6.31, 9.16)	5.43 (4.48, 7.39)	0.000
RV end diastolic area (n=237)	18.98 (16.46, 23.01)	19.80 (15.96, 24.98)	0.343
RV end systolic area (n=237)	9.67 (7.65, 12.16)	9.97 (7.94, 13.25)	0.169
Lateral systolic myocardial velocity (n=199)	6.54 (5.55, 7.73)	6.22 (5.19, 7.54)	0.189
Septal systolic myocardial velocity (n=222)	6.12 (5.09, 6.74)	5.33 (4.57, 6.30)	0.004

Left atrial area (n=286)	18.71 (16.06, 22.90)	20.42 (17.51, 24.31)	0.006
Mean LV wall thickness (n=315)	1.13 (1.03, 1.25)	1.21 (1.06, 1.33)	0.009
Lv mass (n=315)	203.15 (165.63, 257.79)	217.17 (172.72, 277.64)	0.067
Ejection Fraction (n=319)	61.30 (56.31, 66.48)	58.88 (55.58, 63.44)	0.016
E/Em septal ratio (n=217)	14.83 (11.55, 18.57)	16.70 (13.35, 21.89)	0.015
RV fractional area change (n=237)	0.50 (0.44, 0.55)	0.49 (0.43, 0.54)	0.259
E/Em lateral ratio (n=195)	10.66 (7.91, 14.18)	12.05 (8.39, 16.68)	0.088
Simpson Ejection fraction (n=298)	61.57 (56.76, 66.62)	59.38 (56.03, 63.64)	0.032
Teicholtz end-diastolic volume (n=315)	107.52 (90.29, 129.99)	110.95 (85.88, 128.88)	0.972
Teicholtz end-systolic volume (n=315)	44.89 (34.81, 55.71)	47.83 (35.25, 58.79)	0.398
Teicholtz Ejection fraction (n=315)	58.73 (54.57, 61.49)	57.53 (52.88, 60.20)	0.052
End-diastolic volume (n=298)	97.54 (73.30, 121.41)	90.36 (73.37, 121.80)	0.991
End-systolic volume (n=298)	36.37 (25.37, 47.03)	38.83 (27.27, 49.96)	0.243
LA volume (n=293)	54.43 (42.39, 73.41)	62.16 (49.28, 76.74)	0.019
LV relative wall thickness (n=315)	0.46 (0.42, 0.52)	0.49 (0.44, 0.54)	0.023
MR jet area-to-left atrial area ratio (n=232)	0.04 (0.00, 0.10)	0.08 (0.00, 0.17)	0.006
Stroke volume (n=298)	59.15 (44.88, 74.43)	55.95 (44.98, 68.75)	0.419
Abnormal E' (n=248)	95 (72%)	80 (69.0%)	0.604
Diastolic dysfunction grade (n=209)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.768
Diastolic dysfunction grade (modified Olmsted criteria) (n=167)	2.00 (1.00, 2.00)	2.00 (1.00, 3.00)	0.188
Longitudinal Strain (n=205)	-15.95±3.55	-14.85±3.25	0.024
Abnormal Longitudinal Strain (n=205)	52 (44.1%)	56 (64.4%)	0.004
Quartile of Longitudinal Strain (n=205)	2.00 (1.00, 3.00)	3.00 (2.00, 4.00)	0.013
Moderate or greater aortic stenosis (n=259)	2 (1.5%)	1 (0.8%)	1.000
Moderate aortic regurgitation (n=306)	2 (1.2%)	3 (2.2%)	0.836

Prosthetic valve (n=319)	7 (4.1%)	7 (4.8%)	0.764
Was color doppler missing in study (n=319)	11 (6.4%)	1 (0.7%)	0.007
AV peak velocity (n=259)	141.04 (118.53, 173.48)	137.35 (112.63, 172.28)	0.283
Right ventricular outflow tract velocity time integral (n=189)	17.70 (14.42, 21.27)	16.22 (13.23, 19.35)	0.104
Abnormal relative wall thickness(n=315)	123 (72.8%)	118 (80.8%)	0.093
Pulmonary vascular resistance (n=148)	1.72 (1.47, 2.03)	1.94 (1.64, 2.32)	0.005
Significant valvular disease (n=309)	16 (9.8%)	37 (25.3%)	0.000

E = Early wave of mitral inflow, E'= early diastolic mitral annular velocity, LV= Left ventricle, ESV= end systolic volume, EDV= end diastolic volume.

Table S5. C-index, NRI and IDI for evaluating improvement to predict stroke after adding BNP to scores of CHADS2, CHA2DS2-VASc, R2CHADS2 in different subgroups in patients with Heart Failure with Preserved Ejection Fraction

	Clinical model	Clinical model+BNP	Clinical model VS Clinical model+BNP				
	C-index (95%CI)	C-index (95%CI)	P value for C-index	Continuous NRI (%) (95%CI)	*P* value for NRI	IDI (%) (95%CI)	*P* value for IDI
Excluding patients with AF (n=469)							
CHADS2	0.71 (0.63, 0.79)	0.81 (0.73, 0.89)	0.1044	34.8 (0.4, 60.3)	**0.0270**	2.1 (0.3, 8.8)	**<0.0001**
CHA2DS2-VASc	0.67 (0.54, 0.80)	0.77 (0.67, 0.87)	0.2649	35.6 (1.5, 61.2)	**0.0330**	1.3 (0.2, 9.4)	**0.0270**
R2CHADS2	0.73 (0.62, 0.84)	0.80 (0.69, 0.91)	0.3304	34.8 (0.3, 60.7)	**0.0330**	2.70 (0.3, 13.4)	**0.0070**
Excluding patients from Georgia and Russia (n=695)							
CHADS2	0.67 (0.61, 0.73)	0.78 (0.70, 0.85)	0.0126	36.0 (16.0, 52.3)	**<0.0001**	3.0 (0.8, 6.0)	**0.0130**
CHA2DS2-VASc	0.64 (0.54, 0.73)	0.75 (0.68, 0.81)	0.0434	36.6 (12.0, 53.5)	**0.0070**	2.1 (0.5, 5.8)	**<0.0001**
R2CHADS2	0.69 (0.61, 0.77)	0.78 (0.70, 0.86)	0.0503	36.0 (13.8, 52.3)	**0.0130**	3.2 (0.7, 7.1)	**<0.0001**
Excluding patients using warfarin (n=537)							
CHADS2	0.69 (0.63, 0.76)	0.80 (0.74, 0.87)	0.0499	35.0 (4.3, 59.0)	**0.0130**	2.2 (0.4, 9.2)	**<0.0001**
CHA2DS2-VASc	0.74 (0.63, 0.84)	0.81 (0.74, 0.89)	0.0170	35.7 (5.4, 59.2)	**0.0070**	1.8 (0.30, 10.9)	**0.0070**

R2CHADS2	0.73	0.81	0.1920	35.0	**0.0130**	2.7	**<0.0001**
	(0.64, 0.82)	(0.73, 0.89)		(4.3,59.0)		(0.60,12.0)	

BNP: B-type natriuretic peptide, CI: confidence interval, NRI: net reclassification improvement, IDI: the integrated discrimination improvement, AF: atrial fibrillation.

Table S6. Basic characteristics of patients with Heart Failure with Preserved Ejection Fraction stratified by BNP groups which matched basing propensity score

Variables	BNP≤278 pg/mL (n=313)	BNP >278 pg/mL (n=313)	*P*-value
Random to spironolactone	151 (48.2)	170 (54.3)	0.15
Demographics			
Age, years	73 (65, 80)	72 (64, 79)	0.482
Sex, male	156 (49.8)	166 (53.0)	0.472
Race, white	251 (80.2)	246 (78.6)	0.693
BMI, kg/m^2	33.25 (28.28, 37.59)	31.93 (27.31, 37.67)	0.295
Smoking history	166 (53.0)	173 (55.3)	0.630
Alcohol drinking drinks/week			0.681
0	233 (74.4)	240 (76.7)	
1-5	52 (16.6)	52 (16.6)	
6-10	21 (6.7)	14 (4.5)	
10+	7 (2.2)	7 (2.2)	
Physical examination			
EF, %	58.00 (53.00, 62.00)	58.00 (54.00, 62.00)	0.811
NYHA(III-IV)	124 (39.6)	114 (36.4)	0.459
Heart rate, bpm	68 (60, 75)	69 (62, 76)	0.201
SBP, mmHg	128 (118, 138)	130 (118, 139)	0.813
DBP, mmHg	70 (62, 80)	71 (62, 80)	0.615
GFR, ml/min*1.73m^2	59.98 (50.05, 75.59)	63.44 (48.53, 75.59)	0.363
BNP, pg/ml	168.00 (130.00, 218.00)	475.00 (354.00, 717.00)	<0.001
Comorbidities, n (%)			

Pervious hospitalization for CHF	126 (40.3)	147 (47.0)	0.107
Pervious MI	77 (24.6)	75 (24.0)	0.926
Pervious stroke	37 (11.8)	35 (11.2)	0.900
Pervious CABG	63 (20.1)	61 (19.5)	0.920
Pervious PCI	72 (23.0)	78 (24.9)	0.640
COPD	54 (17.3)	49 (15.7)	0.666
Hypertension	286 (91.4)	285 (91.1)	1.000
Peripheral artery disease	40 (12.8)	39 (12.5)	1.000
Dyslipidemia	234 (74.8)	221 (70.6)	0.282
AF	141 (45.0)	139 (44.4)	0.936
Diabetes	133 (42.5)	147 (47.0)	0.296
Medications, n (%)			
Diuretic	281 (89.8)	278 (88.8)	0.796
ACEI	153 (48.9)	169 (54.0)	0.230
ARB	93 (29.7)	82 (26.2)	0.373
Beta blocker	259 (82.7)	259 (82.7)	1.000
Calcium channel blocker	128 (40.9)	120 (38.3)	0.567
Aspirin	200 (63.9)	185 (59.1)	0.250
Statin	210 (67.1)	193 (61.7)	0.182
Warfarin	113 (36.1)	108 (34.5)	0.738

BMI: body mass index, EF: ejection fraction, NYHA: New York heart function class, bpm: beat per minutes, SBP: systolic blood pressure, DBP: diastolic blood pressure, GFR: estimated glomerular filtration rate, BNP: B-type natriuretic peptide, CHF: chronic heart failure, ,MI: myocardial infarction, CABG: coronary artery bypass grafting ,PCI: Percutaneous coronary intervention, COPD: chronic obstructive pulmonary disease, AF: Atrial fibrillation, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin

receptor blocker.