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ORIGINAL ARTICLE

Direct comparison of prognostic ability of cardiac biomarkers for cardiogenic stroke and clinical outcome in patients with stroke

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Abstract

Despite many recent advances in medicine, cardiogenic stroke is still a health problem with a high mortality rate. Cardiac biomarkers have been reported to be useful indicators for cardiogenic stroke and subsequent cerebrovascular events. However, there are no data directly comparing the cardiac biomarkers in stroke patients. We measured atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hsTnT) levels and performed transthoracic and transesophageal echocardiography in 282 stroke patients. There were 108 cases of cardiogenic stroke and 47 cases of major adverse cardiovascular and cerebrovascular events (MACCE) during the follow-up period. Association with left atrial function and left atrial appendage function appeared somewhat stronger for BNP and NT-proBNP than ANP and hsTnT. Multivariate logistic analysis demonstrated that cardiac biomarkers excluding ANP were significantly associated with cardiogenic stroke in stroke patients, multivariate Cox's proportional hazards regression analysis demonstrated that all biomarkers were significantly associated with MACCE after adjustment for confounding risk factors. Receiver operating characteristic curve analysis showed that the C indices of BNP and NT-proBNP for cardiogenic stroke and MACCE were almost equal, but significantly greater than those of ANP and hsTnT. Both BNP and NT-proBNP levels are useful predictors of cardiogenic stroke and subsequent MACCE superior to ANP and hsTnT in stroke patients.

Keywords Cardiac biomarkers · NT-proBNP · Cardiogenic stroke · Major adverse cardiovascular and cerebrovascular events

Introduction

Despite technical advances in medicine, cardiogenic stroke remains a public health problem associated with high all-cause and cerebrovascular mortality [1–3]. An early and accurate diagnosis of cardiogenic stroke is critical for the initiation of timely and effective treatment and management. ddition, early identification and risk stratification of patients at high risk of stroke would be helpful to prevent cerebrovascular disease and subsequent deaths.

Cardiac biomarkers are hitherto generally used for the diagnosis or assessment of heart diseases [4, 5], and their role was expanded and applied to stroke. BNP and NT-proBNP are released from the atrial and ventricular myocardium after precursor proBNP is cleaved into these forms in response to cardiomyocyte stimulation such as volume overload, pressure overload, and ischemic injury [6]. BNP is an active hormone with vasodilatory and diuretic effects to reduce left ventricular overload [7]. Conversely, NT-proBNP is an inactive form and has a longer half-life than BNP [8]. Atrial natriuretic peptide (ANP) is initially synthesised in the granules of atrial myocardium and its plasma concentration is approximately 5000-fold higher than BNP [9].

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Despite differences in activity and metabolic and excretion pathways, these natriuretic peptides have been reported to be useful indicators for the identification of cardiogenic stroke and cerebrovascular disease in patients with stroke [10, 11]. In addition, the Atherosclerosis Risk in Communities (ARIC) study indicated high-sensitivity cardiac troponin T (hsTnT), a marker for myocardial injury, is associated with incidence of stroke in subjects initially free of stroke [12].

Although cardiac biomarkers are indirect findings for the diagnosis of cardiogenic stroke, in contrast to transesophageal echocardiography, they have the advantage of easy, early, and non-invasive detection and may serve as a tool for the early diagnosis or identification of high-risk patients with acute ischemic stroke, which cardiac biomarker is suitable for the assessment of cardiogenic stroke and subsequent cerebrovascular events in patients with stroke is yet to be determined.

The purpose of the present study was to examine the association of cardiac biomarkers with left atrial function and left atrial appendage function and to directly compare the prognostic ability of cardiac biomarkers for cardiogenic stroke and cerebrovascular events in patients with stroke.

Methods

Ethics statement and study population

The institutional ethics committee of Yamagata University School of Medicine approved the study, and all participants provided written informed consent. The procedures were performed in accordance with the Helsinki Declaration. The study was approved by the institutional ethics committee and all patients gave written informed consent.

This was a prospective study involving 282 patients who were admitted to our hospital for the treatment of acute cerebral infarction. The diagnosis of cardiogenic stroke was made by two neurosurgeons and cardiologists who used the generally accepted National Institute of Neurological Disorders and Stroke clinical categories, referring computed tomography, magnetic resonance imaging, and transesophageal echocardiography (TEE). ddition, the severity of stroke was assessed by an expert neurosurgeon using the US National Institutes of Health Stroke Scale (NIHSS).

TEE and transthoracic echocardiography (TTE) were performed by physicians who were blinded to the biochemical data. Chronic atrial fibrillation (CAF), paroxysmal atrial fibrillation (PAF), and sinus rhythm were determined by Holter electrocardiography and continuous electrocardiogram monitoring during . The diagnoses of hypertension (HT), diabetes mellitus (DM), and hyperlipidemia were established based on medical records or history of medical therapy.

Demographic and clinical data including age, sex, and medications at discharge were collected from patient medical records and interviews.

One patient was excluded from the present study because of the lack of TEE data.

Measurement

HT was defined as systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or antihypertensive medication use. DM was defined as fasting blood glucose ≥ 126 mg/dL, glycosylated haemoglobin A1c ≥ 6.5% (National Glycohaemoglobin Standardization Program), or antidiabetic medication use. Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dL, triglyceride ≥ 150 mg/dL, or anti-hyperlipidemic drug use.

Biochemical markers

Blood samples were obtained before TEE for measuring cardiac biomarkers. These samples were transferred to chilled tubes containing 4.5 mg ethylenediaminetetraacetic acid disodium salt and aprotinin (500 U/mL) and were centrifuged at 1000*g* for 15 min at 4°C. The clarified plasma samples were frozen, stored at – 70 °C, and thawed immediately before the assay was performed. BNP concentrations were measured using a commercially available radioimmunoassay specific for human BNP (BNP-JP abbott, Abbott Japan, Chiba, Japan).

To perform an exact comparison between BNP and NT-proBNP, plasma samples, which were obtained simultaneously, were used for NT-proBNP measurement. NT-proBNP levels were measured by electrochemiluminescene immunoassay using the Elecsys NT-proBNP II on cobas e602 platform (Roche Diagnostics K.K., Tokyo, Japan). Troponin T levels were measured using the Elecys Troponin T hs (Roche Diagnostics K.K., Tokyo, Japan).

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with the Japanese coefficient [13].

Echocardiography

TTE was performed using a Vivid E9 ultrasound instrument (GE Healthcare, Wauwatosa, WI, USA) equipped with a sector transducer. A 5 MHz phased-array multiplane probe was used for TEE. The following parameters were assessed using standard view and techniques: left atrial volume index (LAVI), left atrial ejection fraction (LAEF), Simpson left ventricular ejection fraction (LVEF), left atrial appendage empty velocity (LAA eV), and left atrial appendage (LAA)

area. Left atrial function was assessed by LAVI and LAEF [14]. Left atrial appendage function was assessed by LAA eV and LAA area according to previous reports [15].

Endpoint and follow-up

All participants were prospectively followed up for a median period of 1460 days (interquartile range 1105–1460 days). Patients were followed up using telephone or medical records twice a year until 1460 days. The primary and secondary endpoints were cardiogenic stroke and major adverse cardiovascular and cerebrovascular events (MACCE) including rehospitalization for heart failure, acute coronary syndrome, stroke and transient ischemic attack.

Statistical analysis

The normality of continuous variables was examined using the Shapiro–Wilk test. As ANP, BNP, NT-proBNP and hsTnT were not normally distributed, we used $\log_{10}$ ANP, $\log_{10}$ BNP, $\log_{10}$ NT-proBNP and $\log_{10}$ hsTnT for all analyses. All values are expressed as the mean ± standard deviation. Continuous and categorical variables were compared with *t*tests and hi-square tests, respectively. Simple linear analyses were performed to examine the correlation of ANP, BNP, NT-proBNP and hsTnT with left atrial function and left atrial appendage function. A logistic analysis was performed to determine the risk for cardiogenic stroke; significant risk factors were subsequently assessed by multivariate analysis. Survival curves were constructed with the Kaplan–Meier method and compared using log-rank tests. A Cox proportional hazards regression analysis was performed to determine independent predictors of MACCE, and significant predictors selected in the univariate analysis were assessed by multivariate analysis. The receiver operating characteristic (ROC) curves for cardiogenic stroke and MACCE were constructed and used as a measure of the predictive accuracy of ANP, BNP, NT-proBNP and hsTnT for cardiogenic stroke and MACCE. Differences among four groups based on abnormal BNP and NT-proBNP levels were analysed by analysis of variance (ANOVA) with Tukey's post hoc test. A value of $P < 0.05$ was considered statistically significant. All statistical analyses were performed with a standard programme package (JMP version 12; SAS Institute Inc., Cary, NC, USA).

Results

Comparison of clinical characteristics in patients with and without cardiogenic stroke

The patient's baseline characteristics are shown in Table 1. There were 171 men and 111 women. The mean $\log_{10}$ ANP, $\log_{10}$ BNP, $\log_{10}$ NT-proBNP and $\log_{10}$ hsTnT values were 1.66, 1.81, 2.46, and 1.17, respectively. HT, DM, and hyperlipidemia were identified in 204 (72%), 143 (50%), and 88 (31%) patients, respectively. The mean CHA_2DS_2-VASc score, $CHADS_2$ score, and NIHSS score were 3.5, 2.1, and 3.7, respectively. One hundred eight (38%) patients were diagnosed with cardiogenic stroke.

Patients with cardiogenic stroke were older and had a higher prevalence of CAF and PAF than patients without cardiogenic stroke and had prescriptions for vitamin K antagonist. ddition, patients with cardiogenic stroke had higher CHA_2DS_2-VASc score, $CHADS_2$ score, NIHSS score, $\log_{10}$ ANP, $\log_{10}$ BNP, $\log_{10}$ NT-proBNP, $\log_{10}$ hsTnT, LAVI, and LAA area than those without. The levels of eGFR, LAEF, LVEF, and LAA eV were lower in patients with cardiogenic stroke than in those without. There were no significant differences in sex, body mass index, and prevalence of HT, DM, and smoking status between patients with and without cardiogenic stroke.

Association of cardiac biomarkers with left atrial function and left atrial appendage function

To examine whether cardiac biomarkers serve as diagnosis of cardiogenic stroke, the relationship of cardiac biomarkers with left atrial function and left atrial appendage function was studied. All cardiac biomarkers were significantly correlated to LAVI (Fig. 1a), LAEF (Supplemental Figure 1a), LAAeV (Fig. 1b), and LAA area (Supplemental Figure 1B). Interestingly, an association with left atrial dysfunction and left atrial appendage dysfunction appeared stronger for BNP and NT-proBNP than ANP and hsTnT.

Diagnostic ability of cardiac biomarkers for cardiogenic stroke

To determine risk factors for cardiogenic stroke, we performed univariate and multivariate logistic analyses. In univariate analysis, cardiac biomarkers were significantly associated with cardiogenic stroke. Multivariate logistic analysis demonstrated that BNP, NT-proBNP and hsTnT were significantly associated with cardiogenic stroke after adjusting for age, sex, heart rhythm, smoking, CHA_2DS_2-VASc score, and eGFR (Table 2), but not ANP.

Table 1 Comparison of clinical characteristics between patients with and without cardiogenic stroke

Variables	All subjects $n = 282$	CGS (−) $n = 174$	CGS (+) $n = 108$	*P* value
Age	71 ± 12	69 ± 14	76 ± 9	< 0.0001
Male, *n* (%)	171 (61%)	106 (61%)	65 (60%)	0.9024
BMI, kg/m^2	22.9 ± 3.3	23.1 ± 3.1	22.6 ± 3.8	0.3001
CAF/PAF/SR	75/50/157	6/15/153	69/35/4	< 0.0001
Hypertension, *n* (%)	204 (72%)	123 (71%)	81 (75%)	0.4290
Dyslipidemia, *n* (%)	143 (50%)	98 (56%)	45 (42%)	0.0165
Diabetes mellitus, *n* (%)	88 (31%)	58 (33%)	30 (28%)	0.3256
Smoking, *n* (%)	147 (52%)	97 (56%)	50 (47%)	0.1222
CHA_2DS_2-VASc score	3.5 ± 1.7	3.0 ± 1.7	4.3 ± 1.6	<0.0001
$CHADS_2$ score	2.1 ± 1.2	1.7 ± 1.2	2.8 ± 1.3	< 0.0001
NIHSS	3.7 ± 5.5	2.9 ± 4.8	5.0 ± 6.5	0.0029
Biochemical data				
eGFR (mL/min/1.73m^2)	69 ± 24	71 ± 23	65 ± 24	0.0318
Log BNP	1.81 ± 0.51	1.49 ± 0.56	2.29 ± 0.40	< 0.0001
Log NT-proBNP	2.46 ± 0.62	2.09 ± 0.69	3.07 ± 0.49	< 0.0001
Log ANP	1.66 ± 0.41	1.48 ± 0.39	1.92 ± 0.43	< 0.0001
Log hsTnT	1.17 ± 0.41	1.06 ± 0.39	1.37 ± 0.43	< 0.0001
Transthoracic echocardiogram				
LAVI (mL/m^2)	51 ± 25	35 ± 16	76 ± 35	< 0.0001
LAEF (%)	39 ± 13	50 ± 13	23 ± 12	< 0.0001
LVEF (%)	62 ± 10	64 ± 8	59 ± 13	0.0004
Transesophageal echocardiogram				
LAA eV (cm/s)	0.49 ± 0.20	0.63 ± 0.21	0.27 ± 0.18	< 0.0001
LAA area (cm^2)	4.1 ± 1.5	3.4 ± 1.2	5.3 ± 1.8	< 0.0001
Medications				
Anti-platelet drug, *n* (%)	117 (41%)	79 (45%)	38 (35%)	0.0892
Vitamin K antagonist, *n* (%)	79 (28%)	19 (11%)	60 (56%)	< 0.0001
Statin, *n* (%)	69 (24%)	46 (26%)	23 (21%)	0.3259

Data are expressed as mean ± SD, number (percentage)

ANP atrial natriuretic peptide, *BMI* body mass index, *BNP* brain natriuretic peptide, *CAF* chronic atrial fibrillation, *CGS* cardiogenic stroke, *eGFR* estimated glomerular filtration rate, *hsTnT* high-sensitivity troponin T, *LAAarea* left atrial appendage area, *LAAeV* left atrial appendage empty velocity, *LAEF* left atrial ejection fraction, *LVEF* left ventricular ejection fraction, *LAVI* left atrial volume index, *NIHSS* National Institute of Health Stroke Scale, *NT-proBNP* N-terminal pro brain natriuretic peptide, *PAF* paroxysmal atrial fibrillation, *SR* sinus rhythm

To compare the diagnostic ability of cardiac biomarkers for cardiogenic stroke, we illustrated the ROC curves. The C indices of BNP and NT-proBNP for cardiogenic stroke were significantly greater than those of ANP and hsTnT (Fig. 2). The abnormal cut-off values of BNP, NT-proBNP, and hsTnT were 58.2, 431 pg/mL and 0.011 ng/mL, respectively.

Prognostic ability of cardiac biomarkers for cardiogenic stroke

There were 47 MACCE including 23 stroke/TIAs and 15 heart failures and 9 other cardiovascular events during the follow-up period. To determine risk factors for predicting MACCE, we performed univariate and multivariate logistic analyses. In univariate analysis, cardiac biomarkers were significantly associated with MACCE. Multivariate logistic analysis demonstrated that cardiac biomarkers were significantly associated with MACCE after adjusting for CHA_2DS_2-VASc score, NIHSS score, and eGFR (Table 3). To compare the prognostic ability of cardiac biomarkers for MACCE, we illustrated the ROC curves. The C indices of BNP and NT-proBNP for MACCE were significantly greater than those of ANP and hsTnT (Fig. 3). The abnormal cut-off values of BNP, NT-proBNP and hsTnT were 73.4, 381 pg/mL and 0.021 ng/mL, respectively.

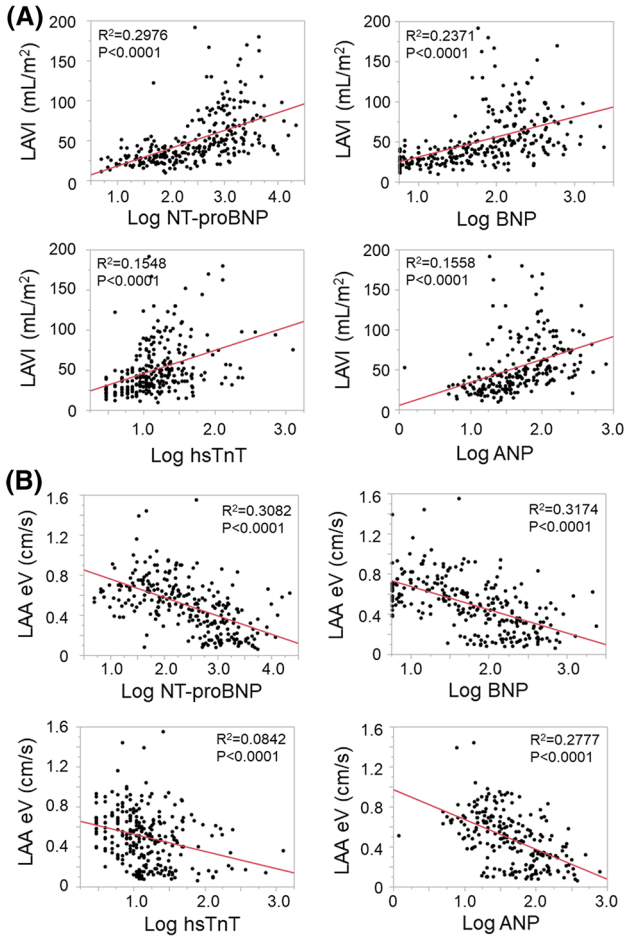

Fig. 1 Associations of BNP/NT-proBNP with LAVI (**a**) and LAA eV (**b**). *LAVI* left atrial volume index, *LAA eV* left atrial appendage empty velocity

Table 2 Univariate and multivariate logistic analyses of predicting cardiogenic stroke

Variables	Odds ratio	95% confidence interval	*P* value
Univariate analysis			
Log BNP	4.725	3.321–7.099	< 0.0001
Log NT-proBNP	4.811	3.400–7.154	< 0.0001
Log ANP	2.927	2.155–4.105	< 0.0001
Lob hsTnT	2.178	1.662–2.931	< 0.0001
Multivariate analysis			
Log BNP	2.796	1.676–4.995	< 0.0001
Log NT-proBNP	2.510	1.557–4.189	0.0001
Log ANP	1.022	0.5982–1.719	0.9312
Log hsTnT	2.038	1.124–3.877	0.0177

After adjustment for age, gender, CHA_2DS_2-VASc score, heart rhythm, smoking, eGFR

ANP atrial natriuretic peptide, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *hsTnT* high-sensitivity troponin T, *NT-proBNP* N-terminal pro brain natriuretic peptide

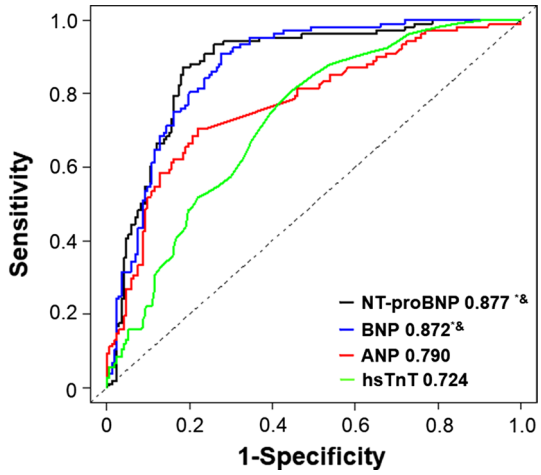

Fig. 2 Receiver operating characteristic curve of cardiac biomarkers for cardiogenic stroke. *ANP* atrial natriuretic peptide, *BNP* brain natriuretic peptide, *hsTnT* high-sensitivity troponin T, *NT-proBNP* N-terminal pro brain natriuretic peptide. $^{*}P < 0.05$ vs. hsTnT, $^{\&}P < 0.05$ vs. ANP

Table 3 Univariate and multivariate Cox proportional hazard analyses of predicting MACCE

Variables	Hazard ratio	95% confidence interval	*P* value
Univariate analysis			
Log BNP	1.865	1.460–2.408	< 0.0001
Log NT-proBNP	1.846	1.444–2.383	< 0.0001
Log ANP	1.642	1.245–2.175	0.0005
Log hsTnT	1.562	1.251–1.978	< 0.0001
Multivariate analysis			
Log BNP	1.736	1.301–2.330	0.0001
Log NT-proBNP	1.750	1.289–2.416	0.0002
Log ANP	1.494	1.092–2.062	0.0130
Log hsTnT	1.409	1.083–1.777	0.0064

After adjustment for CHA_2DS_2-VASc score, NIHSS, and eGFR

ANP atrial natriuretic peptide, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *hsTnT* high-sensitivity troponin T, *NIHSS* National Institute of Health Stroke Scale, *NT-proBNP* N-terminal pro brain natriuretic peptide, *MACCE* major adverse cardiovascular and cerebrovascular disease

Difference between BNP and NT-proBNP

Next, we focused on the difference between BNP and NT-proBNP. We examined the relationship between BNP and NT-proBNP. As shown in Supplemental Figure 2, there was a good correlation between $\log_{10}$ BNP and $\log_{10}$ NT-proBNP.

Kaplan–Meier analysis demonstrated that patients with high BNP had a higher rate of MACCE than those with low BNP. Similarly, Kaplan–Meier analysis demonstrated that

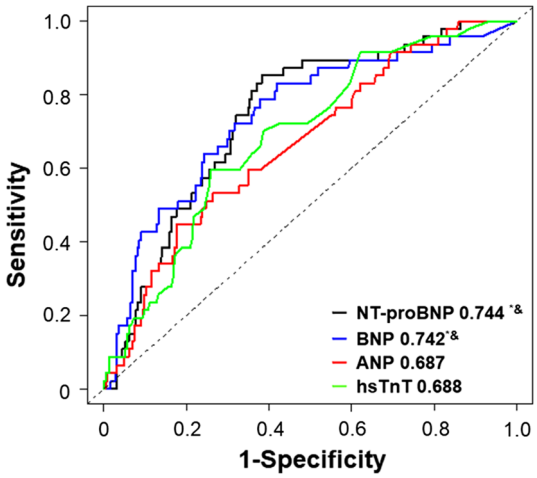

Fig. 3 Receiver operating characteristic curve of cardiac biomarkers for major adverse cardiovascular and cerebrovascular events. *ANP* atrial natriuretic peptide, *BNP* brain natriuretic peptide, *hsTnT*, high-sensitivity troponin T, *MACCE*, major adverse cardiovascular and cerebrovascular events, *NT-proBNP*, N-terminal pro brain natriuretic peptide. $^{*}P < 0.05$ vs. hsTnT, $^{\&}P < 0.05$ vs. ANP

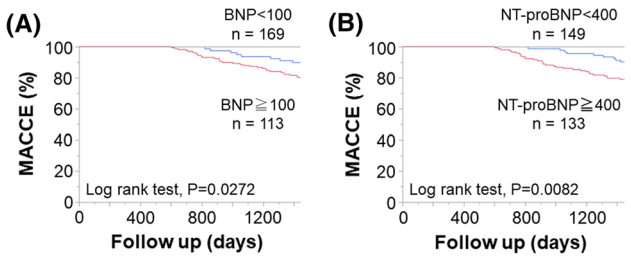

Fig. 4 Kaplan–Meier analyses of BNP (**a**) and NT-proBNP (**b**) for MACCE. MACCE, major adverse cardiovascular and cerebrovascular event

patients with high NT-proBNP had a higher rate of MACCE than those with low NT-proBNP (Fig. 4).

All patients were divided into 4 groups based on abnormal levels of BNP (≥ 100 pg/mL) and NT-proBNP (≥ 400 pg/mL) according to the following heart failure guideline: high-BNP/NT-proBNP group, $n = 102$ (BNP ≥ 100 pg/mL and NT-proBNP ≥ 400 pg/mL); high-NT-proBNP group, $n = 31$ (BNP < 100 pg/mL and NT-proBNP ≥ 400 pg/mL); high-BNP group, $n = 11$ (BNP ≥ 100 pg/mL and NT-proBNP < 400 pg/mL); and control group, $n = 138$ (BNP < 100 pg/mL and NT-proBNP < 400 pg/mL).

As shown in Table 4, the patients in the high-BNP/NT-proBNP group were older and had a higher prevalence of cardiogenic stroke, CAF, PAF, HT, and MACCE than those in other groups. ddition, the patients in this group had higher CHA_2DS_2-VASc score, $CHADS_2$ score, NIHSS score, $\log_{10}$ hsTnT, LAVI, and LAA area and lower LAEF, LVEF, and LAA eV levels than those in other groups. Patients in the high-NT-proBNP group were older and had higher CHA_2DS_2-VASc score, $CHADS_2$ score, $\log_{10}$ hsTnT, LAVI, and LAA area and lower LAEF and LAA eV than those in the control group. Patients in the high-BNP group were older and had higher LAVI and lower LAEF than those in the control group.

Discussion

Main findings

The results of this study revealed four novel findings: (1) BNP and NT-proBNP levels were strongly correlated to left atrial function and left atrial appendage function rather than ANP and hsTnT in patients with stroke(2) although cardiac biomarkers were useful indicators in predicting cardiogenic stroke and MACCE, ROC analyses demonstrated that C indices of BNP and NT-proBNP were significantly greater than ANP and hsTnT(3) Kaplan–Meier analysis demonstrated that patients with high BNP (≥ 100 pg/mL) or high NT-proBNP (≥ 400 pg/mL) had a higher rate of MACCE than patients with stroke(4) both the high-NT-proBNP and high-BNP/NT-proBNP groups had a higher prevalence of cardiogenic stroke and MACCE.

Recent report indicated the relationship between conventional troponin elevation and cardioembolic stroke [16]. There has been no report directly comparing the diagnostic value of cardiac biomarkers for cardiogenic stroke in patients with stroke until now. Unfortunately, the associations of troponin level with left atrial function, left atrial appendage function and cardiogenic stroke were relatively weak compared to BNP and NT-proBNP level in the present study. Furthermore, although troponin elevation was associated with MACCE similar to previous report [17], hsTnT was not superior to BNP and NT-proBNP in predicting MACCE. The association of ANP with mortality was also reported in patients with stroke [18]. Different form other cardiac biomarkers, significant association between ANP and cardiogenic stroke was not persisted after multivariate adjustment. It was reported that BNP and NT-proBNP were useful indicators for cardiac events superior to ANP in patients with cardiac disease such as heart failure and ischemic heart disease [19]. The potential mechanism of the different prognostic ability between ANP and BNP was explained by the fact that BNP secretion is greater than ANP after cardiac stress [20]. Furthermore, it was reported that ANP is decreased with the progression of atrial fibrosis in AF patients who underwent maze procedure [21, 22]. Therefore, difference in the relationship between natriuretic peptide and atrial function may be derived from the secretion amount of natriuretic peptide secondary to induced cardiac stress. In the light

Table 4 Comparison of clinical characteristics among four groups divided by BNP and NT-proBNP levels

Variables	Control group BNP < 100 NT-pro BNP < 400 *n* = 138	BNP high group BNP ≥ 100 NT-pro BNP < 400 *n* = 11	NT-proBNP high group BNP < 100 NT-pro BNP ≥ 400 *n* = 31	BNP/NT-proBNP high group BNP ≥ 100 NT-pro BNP ≥ 400 *n* = 102
Age	67 ± 13	79 ± 5*	76 ± 11*	76 ± 10*
Male, *n* (%)	90 (65%)	5 (45%)	18 (58%)	58 (57%)
BMI, kg/m^2	22.9 ± 3.3	23.1 ± 3.0	22.6 ± 3.8	22.6 ± 3.8
Cardiogenic stroke, *n* (%)	9 (7%)	4 (36%)	17 (55%)	78 (77%)$^{\&}$
CAF/PAF/SR, *n*	3/12/123	2/5/4	16/5/10	54/28/20$^{\&}$
Hypertension, *n* (%)	91 (66%)	9 (81%)	20 (65%)	84 (82%)$^{\&}$
Dyslipidemia, *n* (%)	81 (59%)	4 (36%)	16 (52%)	42 (41%)$^{\&}$
Diabetes mellitus, *n* (%)	45 (33%)	3 (27%)	6 (19%)	34 (33%)
Smoking, *n* (%)	82 (59%)	4 (36%)	14 (45%)	47 (46%)
CHA_2DS_2-VASc score	2.7 ± 1.7	3.7 ± 1.1	4.0 ± 1.3*	4.3 ± 1.7*
$CHDAS_2$ score	1.6 ± 1.2	1.9 ± 0.8	2.5 ± 1.2*	2.8 ± 1.3*
NIHSS	2.5 ± 4.6	2.5 ± 2.3	4.2 ± 6.3	5.4 ± 6.4*
Biochemical data				
eGFR (mL/min/1.73m^2)	72 ± 22	72 ± 11	63 ± 27	65 ± 25
Log hsTnT	0.96 ± 0.32	1.10 ± 0.32	1.31 ± 0.46*	1.43 ± 0.43*
Transthoracic echocardiogram				
LAVI (mL/m^2)	32 ± 18	57 ± 31*	74 ± 46*	67 ± 28*
LAEF (%)	51 ± 13	31 ± 15*	32 ± 19*	27 ± 14*
LVEF (%)	64 ± 8	64 ± 9	62 ± 8	59 ± 13*
Transesophageal echocardiogram				
LAA eV (cm/s)	0.64 ± 0.21	0.54 ± 0.25	0.39 ± 0.33*	0.32 ± 0.18*$^{\$}$
LAA area (cm^2)	3.3 ± 1.2	3.8 ± 1.2	4.6 ± 1.8*	5.0 ± 1.8*
MACCE, *n* (%)	6 (4%)	1 (9%)	7 (15%)	33 (32%)$^{\&}$

Data are expressed as mean ± SD, number (percentage)

BMI Body Mass Index, *BNP* brain natriuretic peptide, *CAF* chronic atrial fibrillation, *eGFR* estimated glomerular filtration rate, *hsTnT* high-sensitivity troponin T, *LAAarea* left atrial appendage area, *LAAeV* left atrial appendage empty velocity, *LAEF* left atrial ejection fraction, LVEF left ventricular ejection fraction, *LAVI* left atrial volume index, *MACCE* major adverse cardiovascular and cerebrovascular event, *NIHSS* National Institute of Health Stroke Scale, *NT-proBNP* N-terminal pro brain natriuretic peptide, *PAF* paroxysmal atrial fibrillation, *SR* sinus rhythm

*$P < 0.01$ vs. control group, $^{\$}P < 0.01$ vs. BNP high group, $^{\#}P < 0.01$ vs. NT-proBNP high group by ANOVA with Tukey's post hoc test, $^{\&}P < 0.05$ by Chi-square test

of these results, we speculated that BNP and NT-proBNP could be more suitable marker for cardiogenic stroke and MACCE in patients with stroke.

The studies comparing the prognostic ability of BNP and NT-proBNP revealed that NT-proBNP is a superior prognostic marker for predicting cardiovascular events in patients with heart failure [23, 24]. A meta-analysis indicated the possibility that NT-proBNP has a superior prognostic capacity for cardiogenic stroke and mortality in patients with stroke [10, 11]. Although these studies included a large population, they directly compare neither the diagnostic nor prognostic ability of BNP and NT-proBNP. Therefore, in this study, we directly compared them and found no significant differences in the diagnostic and prognostic ability of BNP and NT-proBNP. Both peptides can aid in the diagnosis of cardiogenic stroke and prediction of MACCE in patients with stroke.

Cardiac examination and cardiologist consultation are recommended for patients with higher natriuretic peptide levels (BNP ≥ 100 pg/mL and NT-proBNP ≥ 400 pg/mL) according to the Japanese Heart Failure Society. Kristensen et al. reported that NT-proBNP was increased in the presence of AF and that a NT-proBNP level greater than 400 pg/mL was useful to predict clinical outcome in patients with heart failure and reduced ejection fraction, irrespective of AF presence [25]. The cut-off values of NT-proBNP for cardiogenic stroke and MACCE were 431 and 381 pg/mL, respectively. Considering the abnormal cut-off values, we

speculated that NT-proBNP is used as a cognitively descriptive indicator in cardiogenic stroke for physicians, as it was almost equal to that in heart failure. Conversely, the cut-off values of BNP for cardiogenic stroke and MACCE were 58.2 and 73.4 pg/mL, respectively; these values were obviously lower than those for heart failure.

It has been reported that NT-proBNP was associated with AF-related stroke [26]. Similarly, BNP was reported to be associated with left atrial and left atrial appendage dysfunction [27]. Consistent with previous reports, we reconfirmed that both peptides were significantly correlated to left atrial and left atrial appendage dysfunction in patients with stroke. Subgroup analysis showed that 10% of patients had high NT-proBNP level (≥ 400 pg/mL) and low BNP level (< 100 pg/mL). Surprisingly, these patients showed left atrial and left atrial appendage dysfunction and had a higher prevalence of cardiogenic stroke and MACCE. The high-BNP group showed relatively weak relationship with left atrial dysfunction and left atrial appendage dysfunction. NT-proBNP level may be more closely related to left atrial and left atrial appendage dysfunction compared to BNP level.

Recently, LCZ696, a new therapeutic drug for heart failure, has been given a class I recommendation for patients with heart failure with reduced ejection fraction based on the American Heart Association and European Society of Cardiology guidelines [28]. The Prospective Comparison of angiotensin-receptor-neprilysin inhibitor (ARNI) with angiotensin-converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial demonstrated that BNP level increased and NT-proBNP level decreased after administration of LCZ696 [29]. As BNP is a substrate for LCZ696, the diagnostic and prognostic roles of NT-proBNP are gaining attention in patients with heart failure. Because heart failure contributes to the risk of stroke [30], it is expected that the role of NT-proBNP will become more important to predict cardiogenic stroke and MACCE in patients with stroke.

Limitation

This study includes several limitations. First, this is a single-centre study, and the study population was small. Second, as patients were selected and referred to our department to undergo TEE by the neurosurgeon, patients with fatal stroke were potentially excluded. Finally, cut-off values were dependent on the study population, and further study with a larger population is required to determine the optimal cut-off value in patients with stroke.

Conclusions

Both BNP and NT-proBNP levels were strongly correlated to TTE and TEE parameters for LA and LAA function, indicating that these reflect left atrial and left atrial appendage dysfunction in patients with stroke. Direct comparative analysis among cardiac biomarkers showed BNP and NT-proBNP had superior prognostic ability for cardiogenic stroke and MACCE to ANP and hsTnT. Although natriuretic peptide should be carefully considered as the diagnostic or prognostic marker for stroke because of the lack of optimal cut-off values, both BNP and NT-proBNP were highly reliable and clinically useful for predicting the cardiogenic stroke and future cerebrovascular events in patients with stroke.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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