

Original Paper

Brain Natriuretic Peptide Is a Powerful Predictor of Outcome in Stroke Patients with Atrial Fibrillation

Kenji Maruyama^a Shinichiro Uchiyama^{a, c} Tsuyoshi Shiga^b
Mutsumi Iijima^a Kentaro Ishizuka^a Takao Hoshino^a Kazuo Kitagawa^a

^aDepartment of Neurology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan; ^bDepartment of Cardiology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan; ^cClinical Research Center, International University of Health and Welfare, Center for Brain and Cerebral Vessels, Sanno Hospital and Sanno Medical Center, Tokyo, Japan

Keywords

Brain natriuretic peptide · Nonvalvular atrial fibrillation · Stroke · Outcome · Modified Rankin Scale score · Systolic blood pressure · National Institutes of Health Stroke Scale

Abstract

Background: Since stroke patients with nonvalvular atrial fibrillation (NVAf) have poor outcomes in general, the prediction of outcomes following discharge is of utmost concern for these patients. We previously reported that brain natriuretic peptide (BNP) levels were significantly higher in NVAf patients with larger infarcts, higher modified Rankin Scale (mRS) score, and higher CHADS₂ score. In the present study, we evaluated an array of variables, including BNP, in order to determine significant predictors for functional outcome in patients with NVAf after acute ischemic stroke (AIS). **Methods:** A total of 615 consecutive patients with AIS within 48 h of symptom onset, admitted to our hospital between April 2010 and October 2015, were retrospectively searched. Among these patients, we enrolled consecutive patients with NVAf. We evaluated the mRS score 3 months after onset of stroke and investigated associations between mRS score and the following clinical and echocardiographic variables. Categorical variables included male sex, current smoking, alcohol intake, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, peripheral artery disease, use of antiplatelet drugs, anticoagulants, or tissue plasminogen activator (tPA), and infarct size. Continuous variables included age, systolic blood pressure (SBP), diastolic blood pressure, hemoglobin, creatinine, D-dimer, brain natriuretic peptide (BNP), left atrial diameter, left ventricular ejection fraction (EF), and early mitral inflow velocity/diastolic mitral annular velocity

Kenji Maruyama
Department of Neurology
Tokyo Women's Medical University School of Medicine
8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666 (Japan)
E-Mail maruyama.kenji@twmu.ac.jp

(E/e'). We also analyzed the association of prestroke CHADS₂, CHA₂DS₂-VAsC, and R₂CHADS₂ scores, and National Institutes of Health Stroke Scale (NIHSS) score on admission with mRS score 3 months after the onset of stroke. Patients were classified into 2 groups according to mRS score: an mRS score ≤2 was defined as good outcome, an mRS score ≥3 was defined as poor outcome. To clarify the correlations between categorical or continuous variables and mRS score, uni- and multivariate logistic regression models using the stepwise variable selection method were applied. **Results:** Among 157 patients with NVAF after AIS, 63.7% were male and the mean age was 75.9 years. In univariate regression analysis, poor outcome (mRS score ≥3) was associated with use of tPA, infarct size, age, SBP, BNP, EF, and NIHSS score. In multivariate regression analysis, BNP levels (odds ratio [OR] 6.40; 95% confidence interval [CI] 1.26–32.43; *p* = 0.0235) and NIHSS score (OR 2.87; 95% CI 1.84–4.47; *p* < 0.001) were significantly associated with poor outcome (mRS score ≥3) after adjusting for use of tPA, infarct size, age, BNP, EF, and NIHSS score. **Conclusions:** Apart from NIHSS score, BNP was a very useful predictor for long-term outcomes of patients with NVAF after AIS.

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Introduction

Nonvalvular atrial fibrillation (NVAF) is an important risk factor for ischemic stroke especially in the elderly, and is a major cause of cardioembolic stroke (CES) [1]. Indeed, in the Framingham study, NVAF was shown to be an independent risk factor for stroke [2]. NVAF-related stroke is associated with more disabling and fatal outcomes than stroke without NVAF [3]. Since NVAF-associated stroke leads to severe disability or death [4], there is an urgent need for a predictor of long-term outcome in NVAF patients after acute ischemic stroke (AIS). At present there are several predictors of functional outcome in NVAF patients after AIS, including the CHADS₂ [5, 6] and CHA₂DS₂-VAsC scores [5, 7]. In addition, the R₂CHADS₂ score has been shown to be associated with not only severity at onset, but also functional outcome among NVAF patients after AIS [8]. A recent report indicated that plasma D-dimer levels on admission were correlated with both infarction volume and functional outcome [9]. Furthermore, elevated levels of serum BNP were reported to be associated with NVAF, CES, and poststroke mortality [10]. There were additional reports of the predictive value of BNP for outcome in patients with AIS [11, 12]. We also reported that BNP levels were significantly higher in NVAF patients with larger infarcts, higher modified Rankin Scale (mRS) score, and higher CHADS₂ score [12].

In the present study, we evaluated an array of variables, including BNP, in order to determine significant predictors for functional outcome in patients with NVAF after AIS.

Methods

Study Population and Procedure

This study was approved by the institutional ethics committee of our institute. A total of 615 consecutive patients with AIS within 48 h of symptom onset, admitted to the Department of Neurology at Tokyo Women's Medical University Hospital between April 2010 and October 2015, were retrospectively searched.

Subtypes of AIS were diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [13]. Among the 615 AIS patients searched, we extracted data from 168 NVAF patients with CES. Among them, we excluded patients with the following

conditions: (1) dilated cardiomyopathy ($n = 2$), (2) hypertrophic cardiomyopathy ($n = 2$), (3) implantation of cardiac pacemakers ($n = 1$), and (4) embolism due to cardiac catheterization ($n = 1$). Finally, 157 were eligible for analysis. All patients were of East Asian ethnicity.

Clinical Variables

Categorical variables included sex, current smoking, alcohol drinking, hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), persistent atrial fibrillation (AF), coronary artery disease (CAD), peripheral artery disease (PAD), chronic kidney disease (CKD), and use of antiplatelet drugs, anticoagulants, and tissue plasminogen activator (tPA). HT was defined as blood pressure $\geq 140/90$ mm Hg on admission or use of antihypertensive agents. DM was defined as fasting blood glucose ≥ 126 mg/dL or random blood glucose ≥ 200 mg/dL and hemoglobin A1c $\geq 6.4\%$ (National Glycohemoglobin Standardization Program) on admission or use of antidiabetic agents. DL was defined as serum low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol ≤ 40 mg/dL, or serum triglycerides ≥ 150 mg/dL on admission, or use of antihyperlipidemic agents such as statins or fibrates. AF was diagnosed by 24-h ambulatory ECG monitoring performed on admission. CAD was defined as history of any medical treatment for angina pectoris or myocardial infarction. PAD was defined as intermittent claudication and ankle-brachial index < 0.9 . CKD was defined as creatinine clearance < 60 mL/min [14]. Antiplatelet drugs included aspirin, clopidogrel, and cilostazol; anticoagulants included warfarin and direct oral coagulants.

Continuous variables included age, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin, serum creatinine, creatinine clearance, D-dimer, BNP, left atrial diameter (LAD), left ventricular ejection fraction (EF), and E/e'. Creatinine clearance was calculated by the Cockcroft-Gault formula [15]. The measurements of D-dimer, BNP, LAD, EF, and E/e' are described later.

We evaluated the National Institutes of Health Stroke Scale (NIHSS) score for each patient on admission [16]. Outcomes were evaluated using mRS score 3 months after stroke onset [17]. Patients were classified into 2 groups according to mRS score: mRS score ≤ 2 was defined as good outcome, mRS score ≥ 3 was defined as poor outcome. Prestroke CHADS₂ [18], CHA₂DS₂-VASc [19], and R₂CHADS₂ scores [20] were also calculated.

Magnetic Resonance Imaging

Magnetic resonance imaging of the brain was performed with 1.5-Tesla scanners. The areas of hyperintensity on diffusion-weighted images were used to measure infarct sizes. We classified the infarcts into 3 groups: small (S; ≤ 0.3 to 1.5 cm), large (L; more than one-third of the cerebral hemispheres), and medium (M; sizes between S and L). Sizes of S and M infarcts were 0.3–1.5 cm and > 1.5 cm, respectively in the brain stem and the cerebellar hemisphere [12].

Hemostatic Markers

At the time of admission, venous blood samples were collected in order to measure D-dimer levels, which were quantified using the Nampia D-dimer kit (Sekisui Medical Co., Tokyo, Japan).

Brain Natriuretic Peptide

Whole blood samples were collected at the time of admission. Plasma BNP levels were measured using a chemiluminescence enzyme immunoassay (Fujirebio Inc., Tokyo, Japan). The assay used was a sandwich method that uses 2 monoclonal antibodies against human BNP, one recognizing the carboxyl-terminal sequence and the other the ring structure of BNP [21].

Table 1. Baseline characteristics of the 157 patients

Characteristic	
Male sex	87 (55.4%)
Current smoking	19 (12.1%)
Alcohol intake	27 (17.2%)
Hypertension	110 (70.1%)
Diabetes mellitus	42 (26.8%)
Dyslipidemia	60 (38.2%)
Persistent atrial fibrillation	79 (50.3%)
Coronary artery disease	22 (14.0%)
Peripheral artery disease	4 (2.5%)
Use of antiplatelet agents	50 (31.8%)
Use of warfarin	37 (23.6%)
Tissue plasminogen activator	13 (8.3%)
Infarction size	
Small	37 (23.6%)
Medium	83 (52.9%)
Large	36 (22.9%)
Age, years	76.3±10.2
Systolic blood pressure, mm Hg	145.6±29.9
Diastolic blood pressure, mm Hg	82.9±18.3
Hemoglobin	13.3±3.2
Serum creatinine	1.4±1.9
D-dimer, µg/mL	4.3±16.2
Brain natriuretic peptide, pg/mL	203.5 [112.0–392.3]
Left atrial diameter, mm	4.4±1.1
Ejection fraction, %	49.3±7.1
E/e'	14.4±7.9
Prestroke CHADS ₂ score	2.2±1.2
Prestroke CHA ₂ DS ₂ -VASc score	3.6±1.3
Prestroke R ₂ CHADS ₂ score	3.4±1.6
NIHSS score	7.4±7.9

Values are represented as n (%), mean ± standard deviation, or median [interquartile range]. E, early mitral inflow velocity; e', diastolic mitral annular velocity; NIHSS, National Institutes of Health Stroke Scale.

Echocardiography

An experienced sonographer performed the echocardiographic studies with a SONOS 5500 (Philips Medical Systems, Amsterdam, The Netherlands) or an ARTIDA (Toshiba Medical Systems, Tokyo, Japan) ultrasound system equipped with a 2- to 4-MHz phased-array transducer during continuous ECG recording. Left ventricular systolic function was determined on the basis of the EF using the biplane Simpson's method from apical 2- and 4-chamber views [22]. LAD was measured using tomographic echocardiography. Tissue Doppler imaging was used to record mitral annulus velocities at the septal and lateral corners. Early diastolic (E') tissue Doppler velocities were measured, and the left atrial volume was assessed by the modified biplane area-length method and indexed to body surface area. Early mitral inflow velocity (E) was measured using the pulsed wave Doppler method. The tissue Doppler-derived diastolic mitral annular velocity (e') was measured from the septal corner of the mitral annulus in the apical 4-chamber view [23].

Statistical Analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive data were summarized as mean ± SD, median with interquartile range, and

Table 2. Uni- and multivariate logistic regression models with stepwise variable selection methods predictors of poor outcomes

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Male sex	0.74	0.39–1.41	0.356			
Current smoking	1.17	0.44–3.09	0.757			
Alcohol intake	0.75	0.31–1.80	0.658			
Hypertension	1.03	0.51–2.09	0.926			
Diabetes mellitus	0.72	0.34–1.52	0.392			
Dyslipidemia	0.77	0.39–1.49	0.436			
Persistent atrial fibrillation	1.77	0.93–3.40	0.084			
Coronary artery disease	1.37	0.55–3.40	0.494			
Peripheral artery disease	4.91	0.50–48.34	0.172			
Use of antiplatelet agents	1.07	0.54–2.13	0.840			
Use of warfarin	0.95	0.44–2.02	0.885			
Tissue plasminogen activator	6.08	1.60–23.09	0.008	1.24	0.08–18.58	0.875
Infarct size	6.27	3.21–12.23	<0.001	1.19	0.45–3.19	0.724
Age	1.04	1.01–1.08	0.023	1.00	0.94–1.06	0.993
SBP, per 10 mm Hg increase	1.11	0.99–1.25	0.007			
DBP	1.00	0.98–1.02	0.860			
Hemoglobin	0.98	0.88–1.10	0.764			
Serum creatinine	1.03	0.87–1.21	0.748			
D-dimer	1.00	0.98–1.02	0.960			
BNP, per 100 pg/mL increase	4.58	1.88–11.16	<0.001	6.34	1.25–32.18	0.026
Left atrial diameter	0.93	0.66–1.30	0.662			
Ejection fraction	0.93	0.88–0.98	0.011	1.00	0.93–1.98	0.996
E/e'	1.01	0.96–1.06	0.703			
Prestroke CHADS ₂ score	1.10	0.84–1.45	0.496			
Prestroke CHA ₂ DS ₂ -VASc score	1.25	0.98–1.60	0.075			
Prestroke R ₂ CHADS ₂ score	1.03	0.84–1.25	0.804			
NIHSS score, per 4-point increase	3.47	2.30–5.22	<0.001	2.92	1.80–4.75	<0.001

BNP, brain natriuretic peptide; CI, confidence interval; DBP, diastolic blood pressure; E, early mitral inflow velocity; e', diastolic mitral annular velocity; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure.

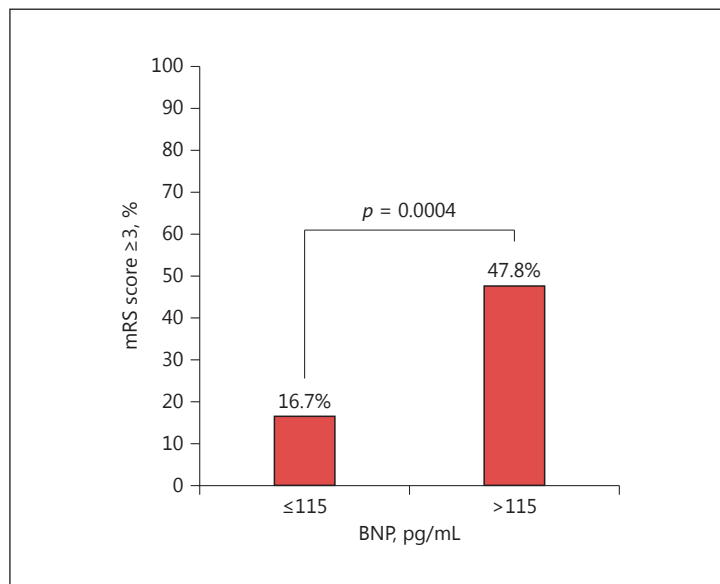
frequency (percentage). The χ^2 test was used to compare variables across nominal categorical variables. To evaluate the impact of potential associated factors with respect to mRS score, both uni- and multivariate logistic regression models with stepwise method were applied. Two-tailed *p* values <0.05 were considered statistically significant.

Results

The patients' baseline characteristics are shown in Table 1. Of 157 patients with NVAf after AIS, 87 (55.4%) were male; the mean age was 76.3 ± 10.2 years. Seventy-nine patients (50.3%) had persistent AF, the remainder had paroxysmal AF. tPA was administered to 13 patients (8.3%). As for infarct size, 37 infarcts were small (23.6%), 83 were medium (52.9%), and 36 were large (22.9%). The mean EF was 49.3 ± 7.1%.

Univariate logistic regression models showed that tPA (odds ratio [OR] 6.08; 95% confidence interval [CI] 1.60–23.09; *p* = 0.008), infarct size (OR 6.27; 95% CI 3.21–12.23; *p* < 0.001), age (OR 1.04; 95% CI 1.01–1.08; *p* = 0.023), SBP (OR 1.11; 95% CI 0.99–1.25; *p* = 0.007), BNP (OR 4.58; 95% CI 1.88–11.16, per 100 pg/mL; *p* < 0.001), EF (OR 0.93; 95% CI

Fig. 1. Correlation between poor functional outcome (mRS score ≥ 3) and BNP level. Higher BNP levels were associated with poor functional outcome (mRS score ≥ 3) 3 months after stroke. mRS, modified Rankin Scale; BNP, brain natriuretic peptide.



0.88–0.98; $p = 0.011$), and NIHSS score (OR 3.47, per 4 points; 95% CI 2.30–5.22; $p < 0.001$) on admission were significantly correlated with mRS score at 3 months. On the other hand, there were no significant correlations of male sex, current smoking, alcohol intake, HT, DM, DL, persistent AF, CAD, PAD, antiplatelet agents, anticoagulants, SBP, DBP, hemoglobin, creatinine, creatinine clearance, CKD, D-dimer, LAD, EF, E/e', prestroke CHADS₂ score, prestroke CHA₂DS₂-VASc score, and prestroke R₂CHADS₂ score with mRS score (Table 2). Multivariate logistic regression models showed that only BNP (OR 6.34; 95% CI 1.25–32.18, per 100 pg/mL; $p = 0.026$) and NIHSS score (OR 2.92; 95% CI 1.8–4.75, per 4-point increase; $p < 0.001$) were significantly correlated with mRS score at 3 months (Table 2). Our findings showed that higher BNP levels are associated with poor functional outcome (Fig. 1).

Discussion

Our study was conducted to find useful predictors for long-term outcome in NVAf patients with AIS. On hospital admission for AIS with NVAf, elevated serum BNP levels and NIHSS score independently predicted functional outcome of patients 3 months after stroke. Therefore, BNP as well as NIHSS score were the most useful predictors of functional outcome in NVAf patients after AIS.

We showed that tPA was associated with good outcome in uni- but not multivariate analysis. In our study, the number of patients treated with tPA was small, and tPA was not always effective because of the greater risk of intracerebral hemorrhage [24]. Infarct size was a significant predictor of outcome in uni- but not multivariate analysis. The outcome after stroke is associated with not only infarct size, but also infarct location [25]. However, we did not analyze the location of infarcts in this study. We previously reported that BNP levels increased as infarct size increased [12], but we did not perform multivariate analysis since the sample size was not big enough for this analysis in our previous study.

HT is an important risk factor [26] and predicts ischemic events in NVAf patients receiving anticoagulant therapy [27]. SBP was shown to be a significant prognostic factor in uni- but not multivariate analysis in this study. It was reported that a high initial SBP after

acute stroke was correlated with poor outcome [28]. The statistical power might not have been enough to show a significant correlation after adjusting confounding factors in our study. Age and NIHSS score have been reported as the most powerful predictors of mortality and functional outcome after ischemic stroke [29, 30]. However, age was significant in uni- but not multivariate analysis in these studies, which was similar to our findings. There was a similar report that NIHSS score more strongly correlated with outcome than age [30]. In previous studies, NIHSS score on admission was shown to be associated with functional outcome 3 months after stroke [31, 32]. Our results were consistent with the results of those studies. However, 1 report suggested that NIHSS score at admission does not always correspond to the outcome 3 months after stroke [33].

Apart from NIHSS score, plasma BNP was the only significant predictor of functional outcome in our NVAF patients after AIS. We demonstrated that BNP levels on admission were positively correlated with mRS score at 3 months in this study. Makikallio et al. [11] also found a relationship between increased BNP levels and mortality in the acute phase of cardioembolism, and ventricular EF and increased LAD were also associated with functional outcome and mortality. LAD was not significantly associated with mRS score in our study. Previously, we reported that serum BNP levels were associated with cardioembolism, infarct size, poor outcome, and risk of stroke in NVAF patients after AIS [12]. Other previous reports showed that BNP levels were associated with diffusion-weighted image lesion size and NIHSS scores on admission [34–36]. We demonstrated that BNP levels were positively correlated with mRS score in both uni- and multivariate analyses in this study. Consistently with our results, a recent report showed that plasma BNP levels were strongly associated with CES and functional outcome 6 months after ischemic stroke [37]. It was reported that in AF, BNP elevation is of atrial origin [38]. It was also reported that BNP level was significantly correlated with left atrial thrombi in AIS with AF [39]. Another study reported that BNP level was significantly correlated with left atrial appendage thrombi, and a stepwise increase in thrombi was significantly associated with a rise in BNP level [40]. We speculated that BNP increase is a reaction to infarction size or is due to cardiac disease. However, all subjects had preserved left ventricular systolic function in transthoracic echocardiography, and BNP was elevated by cardioembolism.

Limitations

Our study has several limitations. First, we retrospectively analyzed the clinical data in a cohort of a single center. Since the statistical power was weak in this study, a larger number of patients are required to provide appropriate conclusions. Second, our assessment of stroke volume was imprecise, evaluating only one slice of diffusion sequence on magnetic resonance imaging where the maximum diameter was detected. Third, timing of BNP measurement does not always correspond with the onset of stroke. Fourth, the risk factors were determined on admission from the patient's medical history. Therefore, prestroke states may not have definitely reflected risk factors.

In conclusions, plasma BNP levels were independently associated with functional outcomes 3 months after stroke onset. Plasma BNP is one of the most useful predictors for long-term functional outcomes of NVAF patients after AIS.

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Disclosure Statement

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