Impact of atrial natriuretic peptide value for predicting paroxysmal atrial fibrillation in ischemic stroke patients

(虚血性脳卒中患者の発作性心房細動検出における心房利尿ペプチドの測定意義)

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Abstracts

Introduction: The impact of atrial natriuretic peptide (ANP) value for predicting paroxysmal atrial fibrillation (pAF) in ischemic stroke patients remains uncertain.

Methods: The consecutive 222 ischemic stroke patients (median 77 [IQR 68-83] years old, 93 females) within 48 hours after onset were retrospectively studied. Plasma ANP and brain natriuretic peptide (BNP) levels were simultaneously measured at admission. Of all, 158 patients had no evidence of atrial fibrillation (AF) (sinus rhythm [SR] group), 25 patients had pAF (pAF group), and the other 39 patients had chronic AF (cAF group). We investigated predicting factors for pAF, with focus on ANP, BNP, and ANP/BNP ratio.

Results: ANP value was significantly higher in the pAF than in the SR group (97 [50-157] mg/dL versus 42 [26-72] mg/dL, $P < 0.05$) and further increased in the cAF group (228 [120-392], $P < 0.05$ versus pAF and SR groups). Similarly, the BNP value was higher in the pAF than in the SR group (116 [70-238] mg/dL versus 34 [14-72] mg/dL, $P < 0.05$) and further increased in the cAF group (269 [199-423], $P < 0.05$ versus pAF and SR groups). ANP/ BNP ratio was lower in the pAF and cAF groups than in the SR group (0.6 [0.5- 1.2] and 0.7 [0.5-1.0] versus 1.3 [0.8-2.4], both $P < 0.05$). Multivariate analysis in the SR and pAF groups (n = 183) demonstrated that age, congestive heart failure, ANP, and BNP, but not ANP/BNP ratio, were independent predictors for detecting pAF. Receiver operating characteristic curve analysis further showed that area under the curve was similar between ANP and BNP (0.76 and 0.80).

Conclusions: ANP may be clinically useful for detecting pAF in ischemic stroke patients as well as BNP.

Introduction

Patients with cardioembolic stroke (CES) are shown to have poor outcome compared to those with other stroke subtypes.[1,2] CES largely occurs in patients with atrial fibrillation (AF) and its risk for incidence of CES can be reduced by anticoagulation therapy.[3] Although it is still controversial whether patients with paroxysmal AF (pAF) have a similar stroke risk to those with persistent AF,[4,5] it is certainly important to identify patients with pAF for preventing occurrence of CES. Furthermore, CES with undetected pAF are often recognized as a cryptogenic stroke.[2] It is reported that AF has been detected in 8.9% of cryptogenic stroke patients by 6 months using an insertable cardiac monitor.[6] Antiplatelet agents, not anticoagulants, may be administered to cryptogenic stroke patients with undetected pAF for secondary prevention, though not effective. Therefore, it is significant importance to detect pAF for primary and secondary prevention of CES.

Plasma brain natriuretic peptide (BNP) levels are shown to be markedly increased in CES patients,[7] and are recognized as a predictor for new AF during hospitalization in patients with acute ischemic stroke.[8] On the other hand, the clinical significance of atrial natriuretic peptide (ANP), a 28 amino acid peptide distributed in the atrium,[9] remains to be determined in ischemic stroke patients. In the present study, we evaluated the usefulness of plasma ANP levels as a predictor of pAF in ischemic stroke patients.

Materials and Methods

Study Patients

From August 2014 to January 2015, a total of 311 acute ischemic stroke patients within 7 days after the onset were admitted to the Hirosaki Stroke and Rehabilitation Center. Of them, 291 patients had a simultaneous measurement of ANP and BNP values on admission. After exclusion of 38 patients admitted more than 48 hours after onset and 31 patients with stroke subtypes other than small artery occlusion, large artery atherosclerosis (LAA), and CES, the remaining 222 patients were included in this study (Figure 1). After admission, heart rhythm of the patients was evaluated by 12-lead electrocardiogram (ECG), monitor ECG, and 24-hour Holter ECG. They were divided into 3 groups: 158 patients with sinus rhythm (SR group), 25 with pAF (pAF group), and 39 with chronic (persistent or permanent) AF (cAF group). We retrospectively investigated factors predicting pAF, with focus on ANP, BNP, and ANP/BNP ratio. This study was approved by the ethics committee of the Hirosaki Stroke and Rehabilitation Center (14A005).

Diagnosis of Ischemic Stroke and Risk Stratification

All ischemic stroke patients underwent brain computed tomography on admission. Unless they had a contraindication, we performed brain magnetic resonance imaging including diffusion-weighted image, T2-weighted image, fluid-attenuated inversion recovery, and magnetic resonance angiography (Signa EXCITED HD 1.5T; GE Medical Systems, Waukesha, WI). Ischemic stroke subtype was determined by 3 stroke neurologists based on the TOAST classification.[10] Branch atheromatous disease was included in LAA in the present study.[11] Carotid ultrasonography, chest X-ray, and standard blood test including HbA1c and D-dimer were performed in all patients. Creatinine clearance was estimated by the Cockcroft– Gault equation. We diagnosed congestive heart failure (CHF) based on left ventricular ejection fraction in echocardiography <40% or New York Heart Association class II or higher heart failure symptom within 6 months before stroke onset.

The $CHADS_2$ score (CHF, hypertension, age [≥75 years old], diabetes mellitus, stroke or transient ischemic attack) and the CHA_2DS_2-VASc score (CHF, hypertension, age [≥75 years old], diabetes mellitus, stroke or transient ischemic attack, vascular disease, age [65-74 year-old], sex category [female gender]) were determined in each patient, as previously described.[12]

Statistical Analysis

Data were shown as median (25th-75th percentiles) or n (%). The Kruskal–Wallis one-way analysis of variance or Fisher's exact test was used to compare differences among the 3 groups. Predicting pAF was assessed by multivariate logistic regression analysis as an odds ratio adjusted for confounding factors using data of SR and pAF groups (n = 183). Receiver operating characteristic (ROC) curve analysis was also performed to evaluate cutoff value, sensitivity, and specificity. Because ANP value, BNP value, and ANP/BNP ratio were not normally distributed, they were logarithmically transformed for logistic regression analysis and ROC analysis. Statistical analyses were performed using JMP 12 software (SAS, Cary, NC). A *P* value less than .05 was considered statistically significant.

Results

Patient Profiles

Clinical characteristics of the study patients are summarized in Table 1. The median age was younger in the SR group than in the other groups. Regarding stroke subtypes, 50% of the patients showed LAA, whereas 24% and 26% had small artery occlusion and CES, respectively. There were 2 patients with CES in the SR group showing paradoxical brain embolism due to

patent foramen ovale and left ventricular thrombosis with old myocardial infarction. There were significant differences in $CHADS_2$ and CHA_2DS_2-VASc scores among the 3 groups. The patients in the SR group had lower scores compared with those in the pAF and cAF groups. Also, there were few patients with CHF in the SR group, whereas there were 20%-30% with CHF in the pAF and cAF groups. Creatinine clearance was the highest in the SR group, followed by the pAF and cAF groups. There was no difference in the HbA1c value on admission among the 3 groups. D-dimer value was the highest in the cAF group, followed by the pAF and SR groups. Transthoracic echocardiography was performed in 144 (65%) patients. Left atrial diameter was greater and left ventricular ejection fraction was lower in the cAF group than in the SR and pAF groups.

ANP, BNP, and ANP/BNP Ratio in Each Group

ANP, BNP, and ANP/BNP ratio on admission are shown in Figure 2. ANP value was significantly higher in the pAF group than in the SR group (97 [50-157] mg/dL versus 42 [26-72] mg/dL, $P < 0.05$) and was further increased in the cAF group (228 [120-392] mg/dL, $P < 0.05$ versus pAF and SR groups). Similarly, BNP value was also significantly higher in the pAF group than in the SR group (116 [70-238] mg/dL versus 34 [14-72] mg/dL, $P < 0.05$) and was further increased in the cAF group (269 [199-423] mg/dL, $P < 0.05$ versus pAF and SR groups). ANP/BNP ratio was significantly lower in the pAF and cAF groups than in the SR group (0.6 [0.5-1.2] and 0.7 [0.5-1.0] versus 1.3 [0.8-2.4], both $P < 0.05$). The ratio did not differ between the pAF and cAF groups.

Univariate and Multivariate Analyses for Detecting pAF

Univariate analysis for pAF using data of the SR and pAF groups (n = 183) showed that age, CHF, creatinine clearance, log ANP, log BNP, and log ANP/BNP ratio were significant (Table 2). Because there was a strong positive correlation between log ANP and log BNP values (r = 0.78, $P < 0.0001$), multivariate analyses were performed separately in Model 1 (log ANP), Model 2 (log BNP), and Model 3 (log ANP/BNP ratio) after adjusting for age, sex, and significant factors shown in univariate analysis (Table 2). In Model 1, age, CHF, and log ANP (odds ratio [OR] 6.25, 95% confidence interval [CI] 1.53-29.9, $P = 0.01$) were significant. In Model 2, age, CHF, and log BNP (OR 3.64, 95% CI 1.23-11.6, $P = 0.02$) were significant. In Model 3, age and CHF were significant, but not log ANP/BNP ratio (OR 0.76, 95% CI 0.18-3.19, $P = 0.71$).

ROC Curve Analysis

ROC curves for log ANP, log BNP, and log ANP/ BNP are shown in Figure 3A. Area under the curve (AUC), sensitivity, and specificity were 0.76, 92%, and 51% for log ANP ($P < 0.0001$); 0.80, 88%, and 65% for log BNP ($P < 0.0001$); and 0.67, 84%, and 54% for log ANP/BNP ratio ($P = 0.03$), respectively (Figure 3B). Cutoff values were 42.6 mg/dL for ANP, 52.4 mg/dL for BNP, and 1.22 for ANP/BNP ratio.

AUC was compared among log ANP, log BNP, and log ANP/BNP ratio. AUC of log BNP was significantly greater than that of log ANP/BNP ratio (0.80 versus 0.67, $P = 0.02$), but similar to that of log ANP (0.76, $P = 0.31$). AUC of log ANP was greater than that of log ANP/BNP ratio, although not statistically significant (0.76 versus 0.67, $P = 0.28$).

Discussion

Major Findings

In the present study, we found that plasma levels of both ANP and BNP on admission in ischemic stroke patients are significantly higher in patients with pAF than in those with SR. They were further elevated in patients with cAF. Importantly, ANP and BNP values are a significant factor for predicting pAF after adjusting for the confounders and there was no difference in AUC between ANP and BNP in ROC curve analysis. These findings indicate that ANP as well as BNP may be clinically useful for detecting pAF in ischemic stroke patients.

Elevated ANP and BNP Values in pAF and cAF Patients at Admission

ANP is mainly secreted from the atria and BNP is from the left ventricle in subjects with normal ventricular function.[13] Because BNP is released in response to volume expansion and pressure overload, it is recognized as a useful marker for heart failure.[13] Furthermore, both plasma ANP and BNP levels are shown to be increased in pAF and cAF patients with normal left ventricular function.[14] Consistent with this, both plasma ANP and BNP levels on admission are higher in pAF patients than in SR patients, and further elevated in cAF patients in the present study. We and others previously showed that BNP levels are also elevated in patients with acute ischemic stroke, especially in CES patients.[7,15] Consistently, stroke subtype in more than 85% of the pAF and cAF patients is shown to be CES in the present study. Because there is no report showing simultaneous measurement of both plasma ANP and BNP levels in acute ischemic stroke on admission, their levels may be potentially useful for detecting pAF and cAF patients, and for determining stroke subtype in acute ischemic stroke patients.

Usefulness of ANP Value for Detection of pAF

Elevated BNP levels are recognized as a predictor for new AF during hospitalization in patients with acute ischemic stroke.[8] Although elevated ANP levels are also shown to be a predictor of pAF development in patients with CHF,[16] its role in ischemic stroke patients remains undetermined. In the present study, we performed univariate and multivariate analyses using the data of only SR and pAF patients to determine significant predictors for detecting pAF. We found that age, CHF, creatinine clearance, ANP value, BNP value, and ANP/BNP ratio were significant variables for detecting pAF in univariate analysis. Multivariate analysis further showed that age, CHF, ANP value, and BNP value are significant. AUC from ROC curve analysis did not differ between ANP and BNP. These findings indicate that plasma ANP as well as BNP levels on admission may be a useful predictor for predicting pAF in acute ischemic stroke patients.

Low ANP/BNP ratio was shown to be a significant risk factor for AF recurrence after electrical cardioversion in patients with mild CHF.[17] Furthermore, preoperative ANP/BNP ratio was negatively correlated with left atrial fibrosis in patients with mitral valve disease.[14] Consistent with these, the present study showed that ANP/ BNP ratio was significantly lower in the pAF and cAF groups than in the SR group. However, ANP/BNP ratio was not a significant predictor for detecting pAF by multivariate analysis when analyzed in patients in the SR and pAF groups. Left atrial diameter by echocardiography was similar between these 2 groups, indicating that atrial remodeling is also similar between the 2 groups. These may affect the results of the logistic regression analysis for ANP/BNP ratio.

In the Framingham Heart Study, CHF has a high risk of developing AF for each sex (OR 4.5 for men, 5.9 for women).[18] Consistent with this, the present study showed that CHF was found the most in the cAF group, followed by the pAF and SR groups. Importantly, CHF is a

significant and independent predictor for detecting pAF when analyzed in patients in the SR and pAF groups, indicating a potentially significant link between CHF and pAF.

Study Limitations

There are several limitations in the analysis of the present study. First, this is a single-center and small-scale retrospective study, and therefore, generalization of results may be limited. Although sensitivity of ANP and BNP for predicting pAF is relatively high (92% and 88%), their specificity is not so high (51% and 65%) in the present study. The small number of the study patients may affect this result. Second, although we evaluated the heart rhythm of the study patients by several methods, the possibility that we could not detect all pAF in the SR group might not be completely excluded. Further intensive evaluations for heart rhythm such as using an insertable cardiac monitor are warranted. Finally, transthoracic echocardiography was performed only in limited patients. Possible useful echo parameters for detecting pAF might not be involved. Further studies are needed.

Conclusions

Plasma ANP and BNP levels on admission are useful for detecting pAF and cAF, and for determining stroke subtype in acute ischemic stroke patients. Particularly, ANP as well as BNP values are a significant predictor of pAF, indicating that ANP may also be a clinically useful marker for detecting pAF in ischemic stroke patients.

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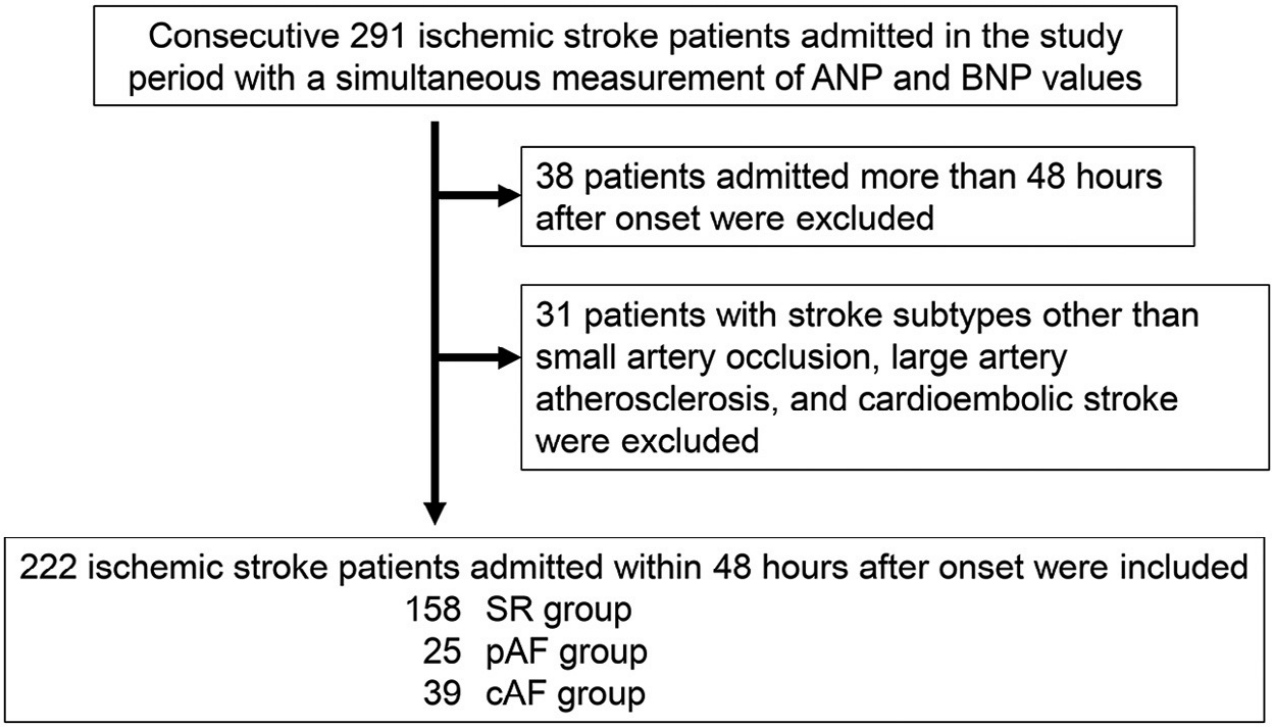


Figure 1. *Flowchart of the study patients.*

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cAF, chronic atrial fibrillation; pAF, paroxysmal atrial fibrillation; SR, sinus rhythm.

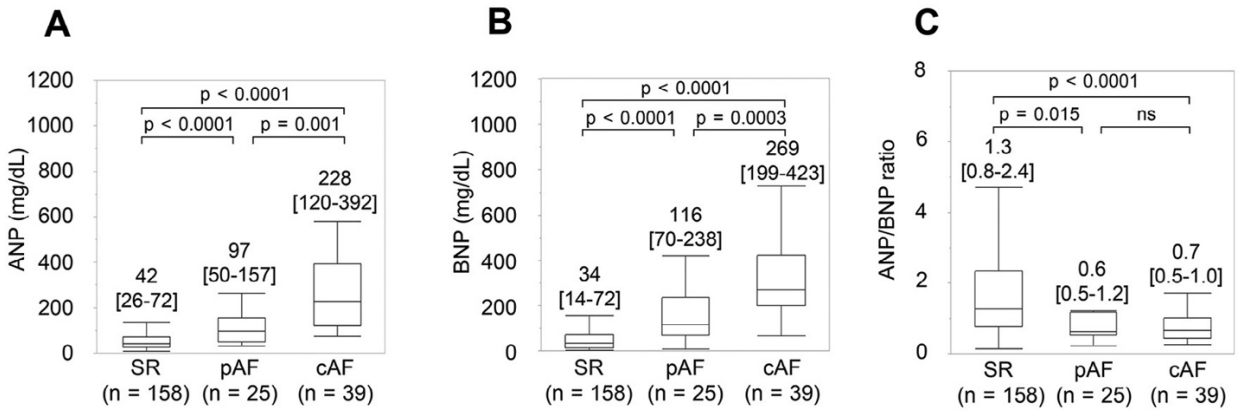
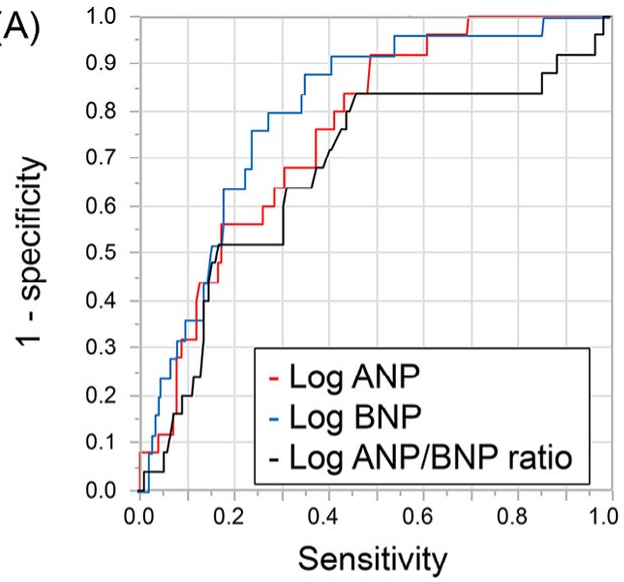


Figure 2. *Comparisons of the ANP (A), BNP (B), and ANP/BNP ratio (C) on admission among 3 groups. Data are shown as median (25th-75th percentiles).*

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cAF, chronic atrial fibrillation; pAF, paroxysmal atrial fibrillation; SR, sinus rhythm.

(A)



(B)

	cut-off value (log)	cut-off value	AUC	sensitivity	specificity
ANP	1.63	42.6	0.76	92%	51%
BNP	1.72	52.4	0.80	88%	65%
ANP/BNP ratio	0.09	1.22	0.67	84%	54%

Figure 3. *ROC curve analyses for log ANP, log BNP, and log ANP/BNP ratio (A) and their cutoff value, area under the curve (AUC), sensitivity, and specificity (B). Data of SR and pAF groups (n = 183) were analyzed.*

Abbreviations: ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; pAF, paroxysmal atrial fibrillation; SR, sinus rhythm.

Table 1. *Clinical characteristics of the study patients*

Variable	Total (n = 222)	SR group (n = 158)	pAF group (n = 25)	cAF group (n = 39)	*P* value
Basic characteristics					
Age (year)	77 [68-83]	74 [65-80]	83 [78-87]	83 [76-87]	<.0001
Female gender	93 (42%)	66 (42%)	11 (44%)	17 (44%)	.96
BMI (kg/m^2)	23.2 [21.0-25.2]	23.3 [21.8-25.2]	24.0 [20.9-25.2]	21.3 [20.0-24.8]	.04
Stroke subtypes					
Small artery occlusion	53 (24%)	51 (32%)	2 (8%)	0 (0%)	
Large artery atherosclerosis	111 (50%)	105 (66%)	1 (4%)	5 (13%)	
Cardioembolic stroke	58 (26%)	2 (1%)	22 (88%)	34 (87%)	
Risk stratification					
Congestive heart failure	20 (9%)	3 (2%)	5 (20%)	12 (31%)	<.0001
Hypertension	182 (82%)	132 (84%)	21 (84%)	29 (74%)	.42
Diabetes mellitus	79 (36%)	63 (40%)	6 (24%)	10 (26%)	.10
Previous stroke or TIA	83 (37%)	55 (35%)	11 (44%)	17 (44%)	.46
Vascular events	37 (17%)	24 (15%)	3 (12%)	10 (26%)	.27
Dyslipidemia	168 (76%)	121 (77%)	20 (80%)	27 (70%)	.56
$CHADS_2$ score	2 [1-4]	2 [1-4]	3 [2-4]	3 [2-4]	.04
CHA_2DS_2-VASc score	4 [3-5]	4 [3-5]	4 [4-6]	5 [4-6]	.01
Blood chemistry					
Creatinine clearance (mL/min)	58 [43-78]	67 [49-86]	52 [42-59]	42 [35-53]	<.0001
HbA1c (%)	5.8 [5.5-6.4]	5.9 [5.5-6.5]	5.6 [5.4-6.3]	5.7 [5.4-6.0]	.16
D-dimer (μg/mL FEU)	.77 [.37-1.49]	.53 [.33-1.03]	1.36 [.72-3.65]	1.54 [.93-3.87]	<.0001
Transthoracic echocardiography					
Number of patients	144 (65%)	98 (62%)	19 (76%)	27 (69%)	
Left atrial diameter (mm)	35 [32-41]	33 [31-38]	36 [32-42]	45 [41-48]	<.0001
Left ventricular ejection fraction (%)	66 [59-71]	67 [61-71]	66 [48-71]	60 [46-66]	.001

Abbreviations: BMI, body mass index; cAF, chronic atrial fibrillation; FEU, fibrinogen equivalent units; pAF, paroxysmal atrial fibrillation; SR, sinus rhythm; TIA; transient ischemic stroke.

Data are shown as median [25th-75th percentiles] or n (%). Creatinine clearance was estimated by the Cockcroft-Gault equation.

Table 2. *Univariate and multivariate analyses for paroxysmal atrial fibrillation in patients in the SR and pAF groups (n = 183)*

	Univariate analysis			Multivariate analyses								
				Model 1			Model 2			Model 3		
Variable	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Basic characteristics												
Age (year)	1.13	1.06-1.21	<.0001	1.12	1.03-1.22	.004	1.13	1.04-1.24	.003	1.13	1.04-1.24	.002
Female gender	1.10	.46-2.56	.83	.45	.15-1.23	.12	.49	.17-1.32	.16	.52	.19-1.37	.19
BMI (kg/m^2)	.98	.85-1.12	.81									
Risk stratification												
Congestive heart failure	12.9	2.95-66.9	.001	7.23	1.45-44.4	.02	5.45	1.03-35.3	.046	11.5	2.14-79.3	.004
Hypertension	1.03	.36-3.76	.95									
Diabetes mellitus	.48	.17-1.20	.12									
Previous stroke or TIA	1.47	.61-3.45	.38									
Vascular events	.76	.17-2.42	.67									
Dyslipidemia	1.22	.46-3.87	.70									
$CHADS_2$ score	1.30	.96-1.77	.09									
CHA_2DS_2-VASc score	1.27	.99-1.63	.051									
Blood chemistry												
Creatinine clearance (mL/min)	.97	.95-.99	.0004	.99	.97-1.03	.98	1.01	.97-1.03	.93	.99	.97-1.02	.73
Log ANP	11.6	3.65-42.0	<.0001	6.25	1.53-29.9	.01						
Log BNP	6.50	2.73-17.4	<.0001				3.64	1.23-11.6	.02			
Log ANP/BNP ratio	.25	.07-0.85	.03							.76	.18-3.19	.71
HbA1c (%)	.64	.35-1.02	.06									
D-dimer (μg/mL FEU)	1.04	.99-1.10	.12									

Abbreviations: ANP, atrial natriuretic peptide; BMI, body mass index; BNP, brain natriuretic peptide; cAF, chronic atrial fibrillation; FEU, fibrinogen equivalent units; pAF, paroxysmal atrial fibrillation; SR, sinus rhythm; TIA, transient ischemic stroke.

Multivariate analyses were performed separately in Model 1 (log ANP), Model 2 (log BNP), and Model 3 (log ANP/BNP) after adjusting for age, sex, and significant factors shown in univariate analysis. Creatinine clearance was estimated by the Cockcroft-Gault equation.