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Original Article

Usefulness of brain natriuretic peptide for predicting left atrial appendage thrombus in patients with unanticoagulated nonvalvular persistent atrial fibrillation

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ABSTRACT

Background: The $CHADS_2$ scoring system is simple and widely accepted for predicting thromboembolism in patients with nonvalvular atrial fibrillation (NVAF). Although congestive heart failure (CHF) is a component of the $CHADS_2$ score, the definition of CHF remains unclear. We previously reported that the presence of CHF was a strong predictor of left atrial appendage (LAA) thrombus. Therefore, the present study aimed to elucidate the relationship between LAA thrombus and the brain natriuretic peptide (BNP) level in patients with unanticoagulated NVAF.

Methods: The study included 524 consecutive patients with NVAF who had undergone transesophageal echocardiography to detect intracardiac thrombus before cardioversion between January 2006 and December 2008, at Hiroshima City Asa Hospital. The exclusion criteria were as follows: paroxysmal atrial fibrillation, unknown BNP levels, prothrombin time international normalized ratio ≥ 2.0, and hospitalization for systemic thromboembolism.

Results: Receiver operating characteristic analysis yielded optimal plasma BNP cut-off levels of 157.1 pg/mL (area under the curve, 0.91; $p < 0.01$) and 251.2 pg/mL (area under the curve, 0.70; $p < 0.01$) for identifying CHF and detecting LAA thrombus, respectively. Multivariate analyses demonstrated that a BNP level > 251.2 pg/mL was an independent predictor of LAA thrombus (odds ratio, 3.51; 95% confidence interval, 1.08–10.7; $p = 0.046$).

Conclusions: In patients with unanticoagulated NVAF, a BNP level > 251.2 pg/mL may be helpful for predicting the incidence of LAA thrombus and may be used as a surrogate marker of CHF. The BNP level is clinically useful for the risk stratification of systemic thromboembolism in patients with unanticoagulated NVAF.

1. Introduction

Systemic thromboembolism, including ischemic stroke and transient ischemic attack, is a serious complication in patients with atrial fibrillation (AF). Several randomized prospective trials investigating nonvalvular atrial fibrillation (NVAF) have confirmed that warfarin administration significantly reduces the risk of stroke, thereby providing a basis for guidelines promoting the use of warfarin in patients with NVAF [1,2]. The congestive heart failure (CHF), hypertension, age, diabetes mellitus, and prior stroke ($CHADS_2$) scoring system is easy for physicians to remember and apply. Additionally, it has been widely validated for risk stratification to predict stroke in patients with NVAF [3]. The $CHADS_2$ score assigns 1 point each for CHF, hypertension, age ≥ 75 years, and diabetes mellitus, and 2 points each for prior stroke or transient ischemic attack. Current guidelines recommend anticoagulant therapy for patients with a $CHADS_2$ score ≥ 2, because the risk of ischemic stroke outweighs the risk of bleeding with anticoagulant therapy [4–6].

Most thrombi associated with NVAF originate in the left atrial appendage (LAA) [7–9]. We previously reported that the serum d-dimer level is clinically useful for guiding the management of patients. In addition, the presence of CHF, a history of embolic

Abbreviations: NVAF, nonvalvular atrial fibrillation; CHF, congestive heart failure; LAA, left atrial appendage; BNP, brain natriuretic peptide; EF, ejection fraction; NYHA, New York Heart Association; TEE, transesophageal echocardiography; PT-INR, prothrombin time international normalized ratio; ROC, receiver operating characteristic; AUC, area under the curve

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events, and the serum d-dimer level are significant predictors of LAA thrombus [10].

Various studies consider CHF as involving the following factors: acute pulmonary edema [3], low ejection fraction (EF) [2,11], New York Heart Association (NYHA) functional classification ≥II [10], and a history of hospitalization for CHF [2,11]. However, the abovementioned clinical criteria are qualitative; therefore, the quantitative definition of CHF remains unclear. Brain natriuretic peptide (BNP) is widely used as a clinical index of the severity of CHF [12]. Therefore, the present study aimed to elucidate the relationship between LAA thrombus and the BNP level and to determine if the BNP level is a quantitative marker of CHF in patients with unanticoagulated NVAF.

2. Material and methods

2.1. Study population

A total of 524 consecutive patients with NVAF who had undergone transesophageal echocardiography (TEE) to detect intracardiac thrombus before cardioversion between January 2006 and December 2008, at Hiroshima City Asa Hospital were enrolled. The study was approved by the Institutional Review Board of Hiroshima City Asa Hospital, and the patients provided consent for inclusion in the study.

Plasma BNP and d-dimer levels were measured simultaneously at the time of TEE. The exclusion criteria were as follows: prothrombin time international normalized ratio (PT-INR) ≥2.0 as a gold standard of warfarin control, paroxysmal AF, organic valvular heart disease, presence of prosthetic valve, and hospitalization due to acute myocardial infarction or systemic thromboembolism, including ischemic stroke and transient ischemic attack. Patients with paroxysmal AF were excluded because its onset could not be determined and its impact on the BNP level was not known.

2.2. Definition of NVAF

According to the guidelines of AF published by the American College of Cardiology, the American Heart Association, and the European Society of Cardiology [13], patients with persistent or permanent AF were included.

2.3. BNP level measurement

All assays were performed at our institution, and all investigators and laboratory personnel were blinded to the clinical status of each patient. Plasma samples for BNP analysis were collected in chilled disposable tubes containing aprotinin (500 kallikrein IU/mL), immediately placed on ice, and centrifuged at 4 °C. Plasma was frozen, aliquoted, and stored at −30 °C until analyzed for the BNP level using a specific immunoradiometric assay for human BNP (Shionogi Co., Ltd., Osaka, Japan).

2.4. TEE examination

TEE was performed using commercially available equipment with a multiplane phase array transducer. Prior to TEE, all participants received a detailed explanation of the procedure and provided written informed consent. A total of 204 patients with AF rhythm underwent TEE. For local anesthesia, lidocaine hydrochloride was administered at the throat for 5 min accompanied by lidocaine hydrochloride spray to anesthetize the posterior pharynx and tongue. The maximum LAA area was measured by tracing a line along the entire endocardial LAA border. The minimal LAA emptying peak flow velocity was measured with a sample volume placed at the entrance of the LAA.

2.5. Identification of LAA thrombus

A thrombus was defined as a circumscribed and uniformly echo-dense intracavitary mass that was distinct from the underlying left atrium or LAA endocardium, and the pectinate muscles in more than 1 imaging plane. Echocardiography technicians were blinded to the plasma BNP level. All TEE data were analyzed independently by 2 cardiologists, and interobserver differences were resolved by a third cardiologist.

2.6. Statistical analysis

Continuous variables were compared using the Mann–Whitney *U*-test, and categorical variables were compared using the chi-square or Fisher's exact test where appropriate. Continuous variables are expressed as median (interquartile range), and categorical variables as numbers and percentages. The optimal cut-off level of BNP for predicting LAA thrombus was calculated by using receiver operating characteristic (ROC) curve analysis. The Person product-moment correlation coefficient was used to evaluate the associations of the plasma BNP level with the plasma D-dimer level and LAA velocity.

Univariate logistic regression analysis was used to determine the associations of clinical and laboratory variables with the presence of LAA thrombus. Furthermore, multivariate logistic regression analysis adjusted for BNP, CHF, and EF was performed to identify independent clinical predictors of LAA thrombus. CHF (i.e., NYHA classification ≥II) was considered as the gold standard for the multivariate analysis. The level of significance for all analyses was set at $p < 0.05$. All analyses were performed using JMP® Statistical Analysis Software (version 8.0.1J, SAS Institute, Cary, NC, USA).

3. Results

3.1. Clinical characteristics of the study population

Among the 524 consecutive patients examined using TEE between 2006 and 2012, 204 were included in the study. The study flowchart is presented in Fig. 1. The median age of the patients was 69 years (interquartile range, 63–75 years), and 58 (28.4%) were women. Moreover, 143 patients (70.1%) had hypertension, 132 (64.7%) had CHF (NYHA classification ≥II), 51 (25.0%) had diabetes mellitus, and 30 (25.0%) had thromboembolism. The prevalence of warfarin treatment was 20.6%.

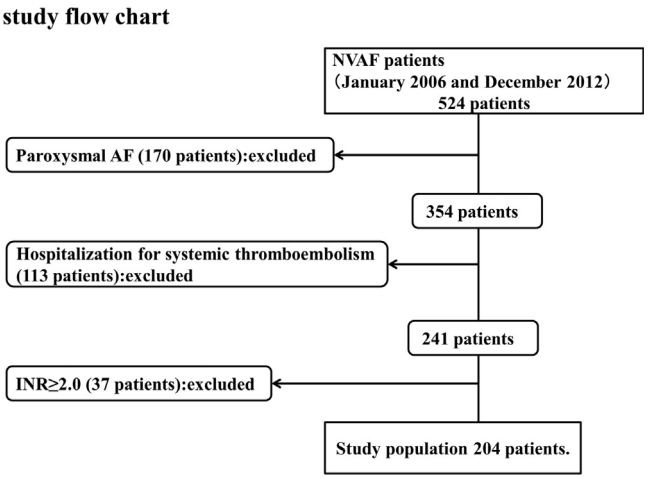

Fig. 1. Flowchart depicting the inclusion of patients in this study. NVAF, nonvalvular atrial fibrillation; INR, international normalized ratio.

3.2. Prevalence of LAA thrombus

The clinical characteristics of patients with and those without LAA thrombus are presented in Table 1. LAA thrombi were detected in 30 (14.7%) patients with NVAF. Patients with LAA thrombus had a higher frequency of CHF (NYHA classification ≥II) and higher plasma BNP and D-dimer levels compared to those in patients without LAA thrombus. In contrast, patients with LAA thrombus had lower EF and LAA velocities compared to those in patients without LAA thrombus. The sensitivities of NYHA classifications ≥II and ≥III for predicting LAA thrombus were 83.3% and 63.3%, respectively. The distributions of $CHADS_2$ scores in patients with and those without LAA thrombus are presented in Fig. 2.

3.3. Associations of the BNP level with the D-dimer level and LAA velocity

We investigated the associations of the plasma BNP level with the plasma D-dimer level and LAA velocity. The BNP level was positively associated with the D-dimer level ($p<0.01$, $R^2=0.14$) and negatively associated with peak LAA velocity ($p=0.028$, $R^2=0.25$) (Fig. 3).

3.4. Diagnostic accuracy of the BNP level for predicting LAA thrombus

The optimal plasma cut-off level of BNP for detecting LAA thrombus was 251.2 pg/mL (AUC, 0.70; $p<0.01$; sensitivity, 73.3%; specificity, 69.2%) (Fig. 4). For this cut-off, the negative predictive value was 93% and the positive likelihood ratio was 1.88. Patients with high plasma BNP levels (i.e., >251.2 pg/mL) had higher median plasma D-dimer levels compared to those in patients with low plasma BNP levels (1.40 μg/mL; interquartile range, 0.68–3.02 μg/mL vs. 0.60 μg/mL; interquartile range, 0.50–1.1 μg/mL; $p<0.01$).

3.5. Predictors of the presence of LAA thrombus

Univariate analysis identified a BNP level >251.2 pg/mL, CHF (NYHA classification ≥II), and EF <40.2% (ROC analysis yielded an optimal EF cut-off value of 40.2% for identifying LAA thrombus). Therefore, these variables were entered into the multivariate model. The multivariate analysis demonstrated that a BNP level >251.2 pg/mL was a significant independent predictor of LAA thrombus (odds ratio, 3.15; 95% confidence interval, 1.08–10.7) (Table 2).

4. Discussion

The present study found that the plasma BNP level was higher in patients with LAA thrombus than in those without LAA thrombus. Additionally, the BNP level was negatively associated with peak LAA velocity evaluated using TEE and positively associated with the D-dimer level. Moreover, the optimal plasma cut-off level of BNP for detecting LAA was 251.2 pg/mL, and a plasma BNP level >251.2 pg/mL was an independent predictor of LAA thrombus in patients with unanticoagulated NVAF. Therefore, a plasma BNP level >251.2 pg/mL could be used to differentiate between patients with and those without LAA thrombus.

Patients with NVAF are treated with anticoagulation therapy on the basis of the $CHADS_2$ scoring system because this system is convenient and easy to apply for predicting thromboembolism in these patients. However, for the management of AF, the definition of CHF is unclear in the current guidelines [14,15].

The BNP level is widely used for assessing patients with CHF. An elevated BNP level is correlated with left ventricular systolic and diastolic dysfunction [12,16,17]. Previous studies have demonstrated that the BNP level is associated with left ventricular filling pressure [18,19] and is well correlated with the severity of heart failure [20,21]. Recent clinical reports have shown that blood coagulability is enhanced in patients with AF [22,23]. Jafri et al. [24] reported that patients with severe heart failure with a high norepinephrine level or low EF are more likely to have an activated platelet and coagulation system. In addition to hemostatic

Table 1
Baseline characteristics of patients with and those without left atrial appendage thrombus.

Characteristic	LAA thrombus (−) ($n=174$)	LAA thrombus (+) ($n=30$)	p-Value
Age, years	69 (63–75)	72 (66–77)	0.15
Male sex, n (%)	124 (71.3%)	22 (73.3%)	0.82
Hypertension, n (%)	123 (70.7%)	20 (66.7%)	0.66
Diabetes mellitus, n (%)	45 (25.9%)	6 (20.0%)	0.48
Dyslipidemia, n (%)	84 (48.3%)	11 (36.7%)	0.24
CHF, n (%)	107 (61.5%)	25 (83.3%)	0.015
NYHA, n (%)			0.027
I	67 (38.5%)	5 (16.7%)	
II	44 (25.3%)	6 (20%)	
III	52 (29.9%)	17 (56.7%)	
IV	11 (6.3%)	2 (6.7%)	
History of admission for CHF, n (%)	18 (10.3%)	3 (10.0%)	0.95
History of thromboembolism, n (%)	23 (13.2%)	7 (23.3%)	0.17
eGFR (mL/min/1.73 m²)	66.2 (55.8–77.7)	55.5 (39.3–59.7)	<0.01
BNP (pg/mL)	200.3 (118.2–387.7)	458.9 (216.5–677.8)	<0.01
BNP >251.2 pg/mL, n (%)	68 (39.1%)	22 (73.3%)	<0.01
$CHADS_2$	2.1 (1.9–2.3)	2.6 (2.1–3.1)	0.047
D-dimer (μg/mL)	0.70 (0.50–1.50)	1.80 (1.05–3.45)	<0.01
BMI (kg/m²)	23.8 (21.8–26.8)	23.6 (20.2–25.4)	0.25
EF (%)	53.5 (43.0–60.0)	44.3 (32.6–57.5)	0.022
LAA area (cm²)	6.1 (4.7–7.8)	6.0 (5.0–9.0)	0.27
LAA velocity (cm/s)	29.4 (21.4–43.1)	22.3 (11.2–27.0)	<0.01
INR at the time of TEE	1.02 (0.99–1.15)	1.07 (1.01–1.22)	0.08
Warfarin treatment, n (%)	38 (21.8%)	4 (13.3%)	0.27

CHF, congestive heart failure; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; BMI, body mass index; EF, ejection fraction; LAA, left atrial appendage; TEE, transesophageal echocardiography.

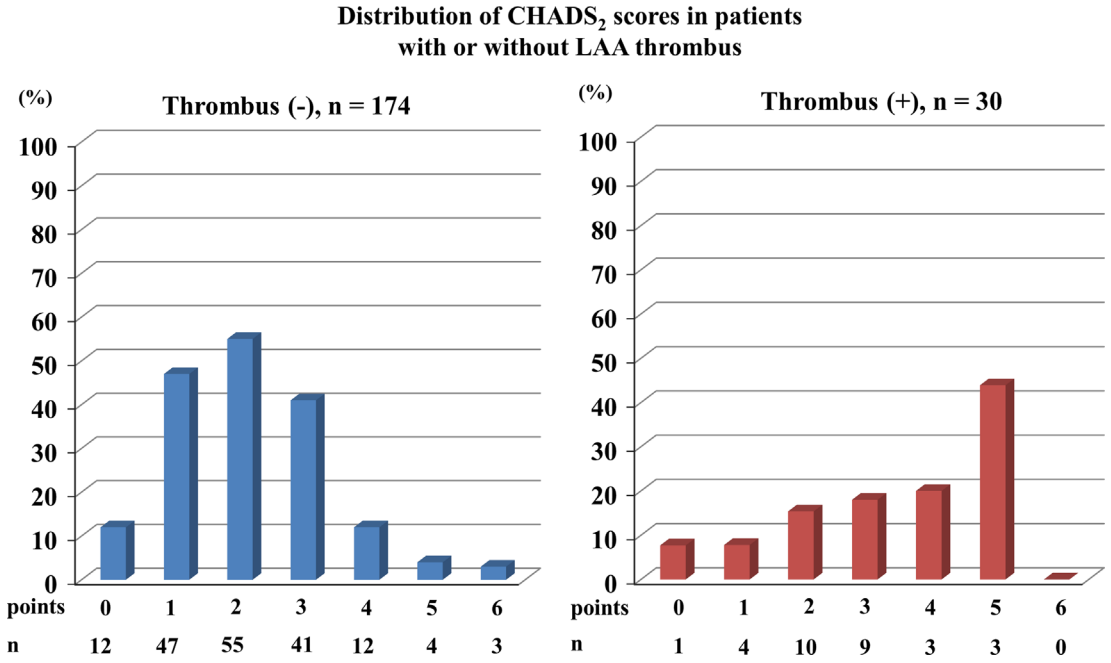

Fig. 2. Distribution of $CHADS_2$ scores in patients with and those without left atrial appendage thrombus. LAA, left atrial appendage.

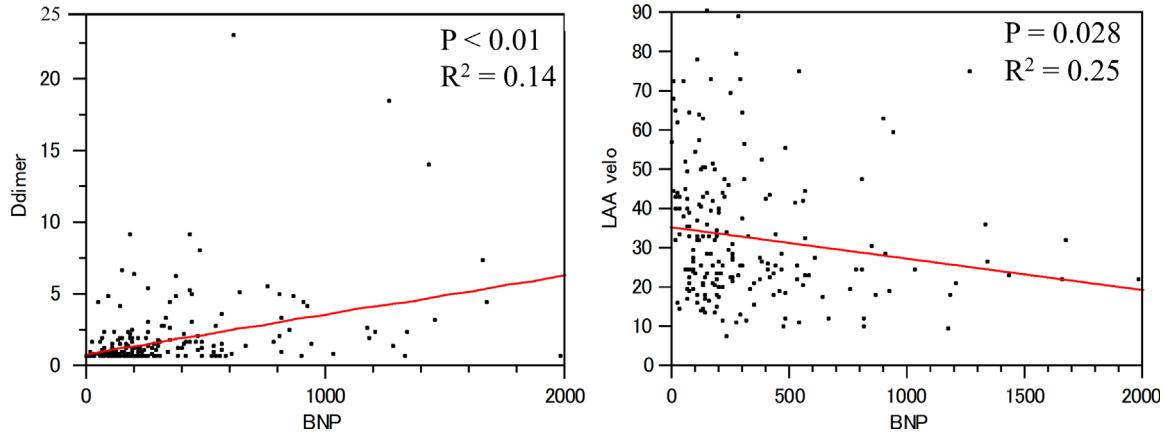

Fig. 3. Correlations of the plasma brain natriuretic peptide level with the plasma D-dimer level and peak velocity of the left atrial appendage.

abnormalities, endothelial dysfunction may contribute to the hypercoagulability observed in patients with CHF [22]. Concordant with these findings, a BNP level >251.2 pg/mL, CHF (NYHA classification $\geq$ II), and systolic dysfunction (EF $<40.2\%$) were significantly associated with the presence of LAA thrombus in the present study.

Watanabe et al. [25] reported that elderly patients with an elevated plasma BNP level have a greater incidence of systemic thromboembolism. LAA thrombus is reported to be associated with the D-dimer level and thromboembolism in patients with NVAF [7–10]. In the present study, a positive association was found between plasma BNP and D-Dimer levels, suggesting that plasma hypercoagulability is closely associated with cardiac dysfunction. Additionally, a negative association was found between the BNP level and peak LAA velocity evaluated by using TEE. Peak LAA velocity measured by using TEE has been proposed for assessing the degree of blood stasis and risk of thromboembolism. These findings indicate that the severity of CHF is associated with a hypercoagulable state possibly from blood stagnation in the LAA.

The results of the present study demonstrate that the BNP level may be a useful surrogate marker for the presence of LAA thrombus. In addition, BNP may be a quantitative and objective marker of risk stratification. In this study, a plasma BNP level >251.2 pg/mL was an independent predictor of LAA thrombus in patients with unanticoagulated NVAF. Therefore, a plasma BNP level >251.2 pg/mL may be useful to differentiate between patients with and those without LAA thrombus, and may provide better identification of high-risk patients with unanticoagulated NVAF. From these perspectives, measuring the BNP level may help in the diagnosis of CHF and the detection of high-risk patients by not only cardiologists but also general physicians. Nevertheless, further prospective clinical studies are required to clarify the impact of the cut-off levels of BNP determined in the present study on the prognosis of patients with NVAF. The present findings will contribute to the prompt detection of unanticoagulated NVAF patients with high risk of thromboembolism.

4.1. Study limitations

This study has some limitations. The study was retrospective and not double-blinded or randomized; therefore, it has the inherent limitations of any single-center retrospective investigation. Although there may have been some bias related to unmeasured factors, we used multivariate analysis to carefully match patients in an effort to eliminate bias. It should be noted that the incidence of LAA thrombus

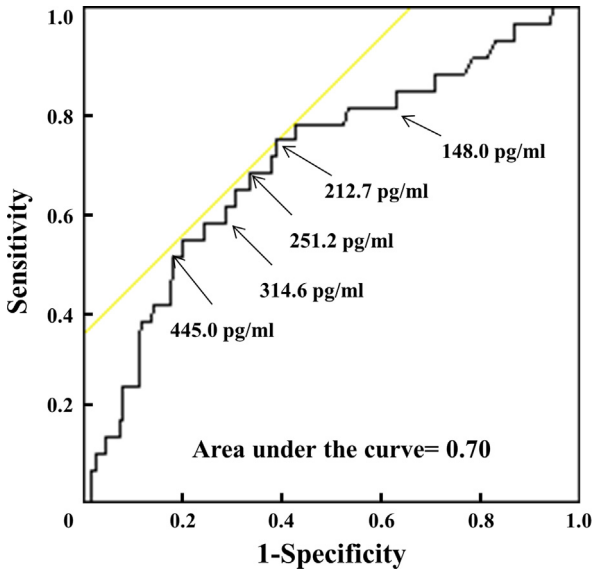

Fig. 4. Receiver operating characteristic curve analysis of the brain natriuretic peptide level for predicting left atrial appendage thrombus. The optimal cut-off level of brain natriuretic peptide was 251.2 pg/mL.

Table 2
Univariate and multivariate analyses adjusted by brain natriuretic peptide level >251.2 pg/mL, congestive heart failure, and ejection fraction $<40.2\%$: risk factors for left atrial appendage thrombus.

Variable	Univariate analysis	Multivariate analysis	
	p-Value	Adjusted odds ratio (95% CI)	*p*-Value
BNP >251.2 pg/mL	<0.01	3.15 (1.08–10.7)	0.046
CHF	0.015	1.16 (0.31–4.46)	0.82
EF $<40.2\%$	0.022	1.62 (0.65–3.99)	0.29
Age ≥ 75 years	0.058		
Hypertension	0.66		
Diabetes mellitus	0.48		
Thromboembolism	0.17		

BNP, brain natriuretic peptide; CHF, congestive heart failure; EF, ejection fraction.

is higher in the present study than in previous studies [1,26,27], because patients with PT-INR ≥ 2.0 were excluded. Additionally, good control of warfarin may have affected the incidence of LAA thrombus. Moreover, in this study, the prevalence of warfarin treatment (20.6%) was lower, and patients admitted for thromboembolism were excluded (including those with a history of systemic thromboembolism). Some patients with paroxysmal AF were excluded in this study because its onset could not be determined and its impact on the BNP level was not known. Therefore, the plasma cut-off level of BNP in this study differed from the cut-off levels determined in previous studies [28,29].

Renal function has been recognized to have a close association with the incidence of stroke [30]. In the present study, eGFR had a strong influence on the presence of LAA thrombus. On multiple logistic regression analysis including eGFR, the statistical significance of BNP disappeared. Originally, eGFR was not included as a risk factor in the CHADS scoring system; therefore, eGFR was excluded from the statistical analysis in the present study.

5. Conclusions

In patients with unanticoagulated NVAF, the BNP level may help predict the incidence of LAA thrombus and may be used as a surrogate marker of CHF in the $CHADS_2$ scoring system. The BNP level is clinically useful for the risk stratification of systemic thromboembolism in patients with unanticoagulated NVAF.

Contributors

All authors were involved in conceiving and designing the study, interpreting the data, and drafting and/or editing the manuscript. All authors have approved the version of the manuscript to be published.

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Conflict of interest

None declared.

Patient consent

Patient consent was obtained.

Ethics approval

Ethics approval was obtained from the Institutional Review Board of Hiroshima City Asa Hospital.

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