Relation Between the CHA2DS2-VASc Score and Left Atrial Appendage Thrombus in Patients with Non-valvular Atrial Fibrillation under Real-world Anticoagulation with Warfarin

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Abstract

Objective: The goal of this study was to investigate the relation between the CHA2DS2-VASc score and left atrial appendage (LAA) thrombus in Japanese patients with NVAF under real-world anticoagulation with warfarin.

Methods: We retrospectively investigated 408 consecutive patients with NVAF who were referred to our hospital between April 2006 and December 2012. After their initial visit to our hospital, all patients had their CHA2DS2-VASc scores calculated and then underwent transthoracic/transesophageal echocardiography (TTE/TEE) for the evaluation of LAA thrombus to facilitate the clinical decision-making regarding anticoagulation, cardioversion, pulmonary vein isolation (PVI) by catheter ablation, or antiarrhythmic drug therapy. We investigated the relationship between the CHA2DS2-VASc score and LAA thrombus and determined the predictor of LAA thrombus by multivariate analysis.

Results: Ninety-one percent of all patients had already received warfarin as part of regular clinical practice, but LAA thrombus was found in 3.7% of the patients with a CHA2DS2-VASc score of 0 or 1 and in 17.3% of the patients with a CHA2DS2-VASc score ≥2 (p < 0.001). The prevalence of LAA thrombus increased with ascending CHA2DS2-VASc score, both in the 215 patients with paroxysmal AF (score 0 [0%], 1 [1.8%], 2 [5.3%], 3 [4.3%], 4–9 [4.7%]) and in the 193 patients with persistent/chronic AF (score 0 [9.4%], 1 [6.5%], 2 [25.6%], 3 [18.2%], 4–9 [39.5%]). On multivariate analysis, a higher CHA2DS2-VASc score, persistent/chronic AF, a history of congestive heart failure (CHF) and of stroke/transient ischemic attack (TIA) were significantly associated with LAA thrombus.

Conclusion: LAA thrombus may occur with greater frequency in high-risk CHA2DS2-VASc score patients. Adequate anticoagulation should be ensured in patients with NVAF who have a CHA2DS2-VASc score ≥2, a history of CHF or stroke/TIA, or the persistent/chronic type of arrhythmia.

Key words
atrial fibrillation, practical clinic anticoagulation, CHA2DS2-VASc score, left atrial appendage thrombus

Abbreviations
NVAF = non-valvular atrial fibrillation; AF = atrial fibrillation; LA = left atrial; LAA = left atrial appendage; TEE = transesophageal echocardiography; SEC = spontaneous echo contrast; LVEF = left ventricular ejection fraction; CCr = creatinine clearance; BNP = brain natriuretic peptide; PT-INR = prothrombin time/international normalized ratio; NSR = normal sinus rhythm

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Introduction

Non-valvular atrial fibrillation (NVAF) is identified as a “common disease” in general clinical practice and associated with a 4–6 fold increase in thromboembolism, presumably from left atrial appendage (LAA) thrombi, which are detected in 7% to 14% of patients with NVAF using transesophageal echocardiography (TEE). Adequate anticoagulation therapy in patients with NVAF is very important to prevent thromboembolism. However, the level of anticoagulation achieved with warfarin is often inadequate to avoid the risk of bleeding, in view of the fact that especially Asians with NVAF were at successively greater intracranial hemorrhage risk than whites. In Japan, where the elderly population is growing rapidly, the prevalence of AF is also high among people aged over 60, exceeding 10% among those in their 80s, and it is expected that the prevalence of AF will reach 1000 per 100,000 population from 2010–2030. Recently, non-vitamin K antagonist oral anticoagulants are widely used. However, warfarin is still useful for renal insufficiency and elderly patients. The CHADS2 score has been proposed for stratifying patients with NVAF according to the risk of thromboembolism. In the Guidelines for the Management of Patients with AF proposed by the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) in 2006, anticoagulation therapy is recommended for a patient with AF who has a CHADS2 score from 2 to 6. In 2010, a newly developed scoring system, the CHA2DS2-VASc score, which extends the CHADS2 score by considering additional stroke risk factors, was recommended by the ESC guideline. The CHA2DS2-VASc score is simple and easy to use, but its relation to the prevalence of LAA thrombus has not been fully clarified in patients with NVAF who are under the anticoagulation with warfarin actually used in Japanese clinical practice. The aim of this study was to investigate the relation between the CHA2DS2-VASc score and LAA thrombus in Japanese patients with NVAF under real-world anticoagulation with warfarin. In addition, we used multivariate analysis to investigate the relationship between LAA thrombus and the clinical predictors included in the CHA2DS2-VASc score, the type of AF, the clinical characteristics, and the level of anticoagulation.

Methods

Patients

We carried out a retrospective evaluation of 408 consecutive patients with NVAF, who were referred between April 2006 and December 2012. After the initial visit to our hospital, all patients underwent transesophageal echocardiography (TEE) for the evaluation of LAA thrombus to facilitate the clinical decision-making regarding anticoagulation, cardioversion, pulmonary vein isolation (PVI) by ablation-, or antiarrhythmic drug therapy. Ninety-one percent of patients in this study had already been taking warfarin as anticoagulant therapy before being referred to our hospital, 71 percent of all patients were anticoagulated on warfarin for ≥4 consecutive weeks prior to TEE, 20 percent of all patients were anticoagulated for <4 weeks, and 9 percent had not taken any warfarin. INR was taken from all patients before TEE. A retrospective medical record review was performed by an observer blind to the echocardiographic findings, including clinical data for the 3 months before the TEE examination, and CHA2DS2-VASc scores (table 1) were calculated for all patients. A low thromboembolic risk was defined as a CHA2DS2-VASc score of 0 to 1. The type of AF was recorded for each patient. Paroxysmal AF was defined as recurrent AF (≥2 episodes) that terminated spontaneously within 7 days. Persistent AF was defined as AF that was sustained beyond 7 days or lasted <7 days but required pharmacologic or electrical cardioversion. Chronic AF was defined as longstanding persistent AF (continuous AF beyond 1 year) for which cardioversion had either failed or not been attempted. This study protocol was approved by the St. Marianna University School of Medicine Institutional Committee (No. 2140).

Echocardiographic data analysis

TEE was performed using a multiplane phase array transducer (Vivid 9, General Electric Company, Milwaukee, Wisconsin). All patients gave written informed consent before undergoing TEE. Lidocaine was used for local anesthesia of the hypopharynx. Conscious sedation with intravenous diazepam was given in all patients. Standard esophageal intubation and TEE acquisition were conducted. Cine loops of the left atrium (LA) and LAA from 0° to 180° were stored for offline analysis. TEE recordings were reviewed for the presence of spontaneous echo contrast (SEC), LAA sludge, and thrombus by 2 observers.
who were blind to the patients’ clinical history. Interobserver differences were resolved by a third observer. SEC was defined as a dynamic “smoke-like” echo with a characteristic swirling motion at the optimal gain setting during a cardiac cycle. Thrombus was defined as a circumscribed and uniformly echodense intracavitary mass, distinct from the underlying LA or LAA endocardium and the pectinate muscles, and present in more than one imaging plane. Sludge and SEC grade 4 were defined as thrombus.

**Statistical analysis**

Summary statistics are expressed as mean± standard deviation for continuous variables and percentages for categorical variables. All patients were divided from 5 groups according to a five-number summary with the CHA2DS2-V ASc score. The non-parametric Wilcoxon-type trend tests for ordered groups were used to test the trends of creatinine clearance (CCr), left ventricular ejection fraction (LVEF), left atrial (LA) diameter, and prothrombin time/international normalized ratio (PT-INR) across the CHA2DS2-V ASc scores (0, 1, 2, 3, and 4–9). Chi-square tests were used to evaluate the differences across the same categories for categorical variables. Multivariable logistic regression models were used to evaluate predictors of LAA thrombus among the clinical parameters, echocardiography findings, and CHA2DS2-V ASc scores. Statistical analyses were performed using the STATA statistical software package (Version 11. College Station, Tex). A two-sided p-value <0.05 was considered statistically significant.

**Results**

**Relationship of CHA2DS2-VASc score and clinical characteristics**

Patient characteristics are shown in Table 1. The mean age of the participants was 63±11 years; 81.6% were men, 52.7% had paroxysmal AF, and 91.4% were anticoagulated with warfarin at the time of TEE. Mean INR was 1.66±0.62. CHA2DS2-VASc scores of 0 and 1 were present in 21.1% and 25.2%, making a total of 46.3% who were at low risk.

**Prevalence of LAA thrombus (Table 2)**

The initial TEE recordings used to screen patients for LAA thrombus were reviewed and compared with the CHA2DS2-VASc scores. Table 2 shows the LAA thrombus prevalence, together with the clinical and echocardiographic characteristics according to the CHA2DS2-VASc scores. There were no significant differences in LA diameter, and all patients had maintained ejection fraction. The prevalence of LAA thrombus increased with ascending CHA2DS2-VASc score (score 0 [3.5%], 1 [3.9%], 2 [18.9%], 3 [13.7%], 4–9 [21.1%]). The INR increased with ascending CHA2DS2-VASc score (score
LAA thrombus relative to CHA2DS2-VASc score and classification of AF

Table 2. Left Atrial Appendage Thrombus Prevalence, Clinical and Echocardiographic Characteristics, According to CHA2DS2-VASc Scores.

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>0 (n = 86)</th>
<th>1 (n = 103)</th>
<th>2 (n = 77)</th>
<th>3 (n = 56)</th>
<th>4-9 (n = 86)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA thrombus (%)</td>
<td>3(3.5%)</td>
<td>4(3.9%)</td>
<td>12(18.9%)</td>
<td>7(13.7%)</td>
<td>19(21.1%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>66±12</td>
<td>68±12</td>
<td>65±12</td>
<td>61±12</td>
<td>65±15</td>
<td>0.02*</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>44±10</td>
<td>42±8</td>
<td>42±8</td>
<td>44±8</td>
<td>44±9</td>
<td>0.919</td>
</tr>
<tr>
<td>CCr (ml/min)</td>
<td>106±24</td>
<td>89±26</td>
<td>81±20</td>
<td>67±22</td>
<td>60±18</td>
<td>0.001*</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.53±0.55</td>
<td>1.64±0.63</td>
<td>1.62±0.61</td>
<td>1.84±0.61</td>
<td>1.7±0.69</td>
<td>0.01*</td>
</tr>
<tr>
<td>use of warfarin (%)</td>
<td>81 (94%)</td>
<td>95 (92%)</td>
<td>70 (91%)</td>
<td>52 (93%)</td>
<td>75 (87%)</td>
<td>0.551</td>
</tr>
<tr>
<td>adequate anticoagulation (%)</td>
<td>13 (15.1%)</td>
<td>21 (20.4%)</td>
<td>20 (26%)</td>
<td>24 (42.9%)</td>
<td>31 (36%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>persistent/chronic AF</td>
<td>32 (37.2%)</td>
<td>46 (44.7%)</td>
<td>39 (50.7%)</td>
<td>33 (59%)</td>
<td>43 (50%)</td>
<td>0.115</td>
</tr>
<tr>
<td>NSR at time of TEE</td>
<td>39 (45%)</td>
<td>44 (43%)</td>
<td>27 (35%)</td>
<td>17 (30%)</td>
<td>32 (37%)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

LAA = left atrial appendage; LVEF = left ventricular ejection fraction; LAD = left atrial diameter; CCr = creatinine clearance; BNP = brain natriuretic peptide; PT-INR = prothrombin time international normalized ratio; AF = atrial fibrillation; NSR = normal sinus rhythm; TEE = transesophageal echocardiography

Figure 1. The prevalence of left atrial appendage thrombus relative to CHA2DS2-VASc scores and classification of atrial fibrillation (AF).

(A) Paroxysmal AF
(B) Persistent/chronic AF

0 [1.53±0.55], 1 [1.64±0.63], 2 [1.62±0.61], 3 [1.84±0.61], 4–9 [1.7±0.69]). However, in many cases the level of anticoagulation was inadequate, since only 26.7% of the patients at the time of TEE had adequate INR reported by Japanese guidelines.

LAA thrombus relative to CHA2DS2-VASc score and classification of AF

In the paroxysmal AF group, 91.2% of patients were taking warfarin as anticoagulation therapy. Their average INR was 1.58±0.59, but only 17.2% of the patients had an adequate INR at the time of TEE. In the persistent/chronic AF group, 91.7% of patients were taking anticoagulant therapy, the average INR was 1.75±0.65, but only 25.4% of the patients had an adequate INR at the time of TEE. In the 215 patients with paroxysmal AF, the prevalence of LAA thrombus increased with ascending CHA2DS2-VASc scores (score 0 [0%], 1 [1.8%], 2 [5.3%], 3 [4.3%], 4–9 [4.7%]), and a similar association was
CHA2DS2-VASc score and left atrial appendage thrombus

In the multivariate logistic regression analysis, persistent/chronic AF (odds ratio [OR] 8.9, 95% confidence interval [CI] 1.27–3.11, p < 0.001) and higher CHA2DS2-VASc scores (OR 1.5, 95% CI 0.14–0.62, p = 0.002) were significantly associated with the prevalence of LAA thrombus (Table 3). On multivariate analysis, a history of CHF and stroke/TIA were independent predictors of LAA thrombus in these patients (Table 4).

Discussion

The specific feature of the present study is that our study included almost all patients with AF who were receiving warfarin. Of 408 consecutive patients, only 109 patients (26.7%) had adequate anticoagulation control reported by Japanese guidelines. We investigated the prevalence of LAA thrombus based on the CHA2DS2-VASc scores. In the higher risk group, defined by a CHA2DS2-VASc score ≥ 2, thrombus formation was not fully prevented in patients receiving warfarin, because most of them had inadequate anticoagulation with warfarin. The Fushimi AF registry is a community-based prospective survey of AF patients in Japan, in which 3378 patients were enrolled from March 2011 to December 2012, and 2395 patients completed a one-year follow-up. In the results of the registry, an anticoagulant drug was prescribed for only 54.7% of patients (52.6% warfarin, 2.1% dabigatran). Thromboembolic events were observed in 69 patients (2.9%). The Fushimi AF Registry shows anticoagulant therapy is not fully established in Japan, and some AF patients may not receive benefits from anticoagulation. The results of our study suggested that LAA thrombus might be present even in patients receiving warfarin, and that anticoagulation alone was insufficient to prevent further embolism when the efficacy of anticoagulation did not reach the target PT-INR.

Nowadays, the ESC guidelines suggest that the initiation of anticoagulant therapy should be determined by the CHA2DS2-VASc score. In the present study, the incidence of LAA thrombus was higher in persistent/chronic AF patients with CHA2DS2-VASc scores of 0 and 1 than in those with paroxysmal AF. In paroxysmal AF, anticoagulant therapy defined by the ESC guidelines is useful; furthermore, this therapy is also required in persistent/chronic AF with inadequate anticoagulation with warfarin.
CHaDS-VASc scores of 0 and 1 because thrombi may be observed even in these patients. In the present study, the CHaDS-VASc score was 0 in 3 persistent/chronic AF patients who revealed thrombi. The pathology of thrombus formation in these 3 patients remains unknown, although the following factors are considered to be possible causes: 1) the mean duration of AF was 1.3 years; 2) the left atrium of the 3 patients was enlarged over 4.3 cm; and 3) 2 patients were not fully anticoagulated with warfarin.

To date, no study has reported an association between the clinical course of AF and the prevalence of LAA thrombus. In fact, not all embolic events with AF are attributable to LAA thrombus; thus, it is important to prevent or dissolve a LAA thrombus by adequate anticoagulation with warfarin. The present study did not investigate the frequency of embolism that might have originated from LAA thrombus; however, the prevalence of LAA thrombus was significantly lower in patients with paroxysmal AF than in those with persistent/chronic AF. The ARISTOTLE study also demonstrated that patients with persistent/chronic AF have a significantly lower incidence of embolism. An earlier large clinical study reported no significant difference in the incidence of embolism between paroxysmal and persistent/chronic AF over a long-term follow-up. The results of our retrospective study suggest different clinical outcomes; however, even paroxysmal AF entails a risk comparable to that of persistent/chronic AF when the arrhythmia is present for a long time. The failure of AF rhythm control leads to persistent/chronic AF, which may trigger thrombosis and embolism. Accordingly, anticoagulant therapy should be taken into consideration even in paroxysmal AF patients who have lower CHaDS-VASc scores, because paroxysmal AF may change to persistent or chronic AF. In general, thrombus formation in the vessels is due to local flow stasis or stagnation, accelerated blood coagulation, and endothelial dysfunction. AF accelerates atrial remodeling, which predisposes the patient to the induction of persistent/chronic AF. In persistent/chronic AF, the loss of the atrial systole impairs ventricular function, leading to LA dilatation. A recent study assessed AF, endothelial dysfunction, and blood-based biomarkers, including transforming growth factor-beta, Von Willebrand factors, and interleukin-6, and investigated their associations with diagnosis and prognosis. The investigators reported that, in persistent/chronic AF, endothelial dysfunction due to LA tissue remodeling and dilatation, accelerated coagulability, and blood flow congestion in the LAA induces thrombus formation. In our study, LAA thrombus was found in persistent/chronic AF patients, suggesting that atrial tissue impairment and endothelial dysfunction caused by persistent/chronic AF might accelerate thrombus formation.

The present study investigated the relation between CHaDS-VASc scores and the incidence of LAA thrombus by TEE. In concordance with earlier reports, our study revealed that the higher the CHaDS-VASc score, the more AF patients exhibited LAA thrombus. The multivariate analysis demonstrated that persistent and chronic AF, and higher CHaDS-VASc scores were closely associated with thrombus formation in the LAA. It also demonstrated that medical histories of cerebral infarction, TIA, and heart failure were risk factors for thrombus formation. A previous study concluded that heart failure and ejection fraction ≤ 35% were predictors of thrombus, which was consistent with our findings. Some studies have already reported the association between CHaDS-VASc scores and LAA thrombus. Puwanant et al. demonstrated that thrombus was found in 0.6% of a total of 1058 cases, representing 0.9% in patients with a CHaDS-VASc score ≥ 2 and 0.5% in those with a CHaDS-VASc score < 2. Their study included patients who were undergoing TEE before pulmonary vein isolation and were fully anticoagulated with a therapeutic INR between 2 and 3.5, which was different from the baseline characteristics of the present study. To our knowledge, the present study was the first to evaluate Japanese AF patients who were not fully treated with anticoagulant therapy. Since a significant number of patients with higher CHaDS-VASc scores revealed LAA thrombus, appropriate anticoagulants should be administered according to the AHA/ESC guidelines. Adequate management is indispensable for patients with persistent AF and those with higher CHaDS-VASc scores; detailed evaluation by TEE and a reduction in stroke risk factors are required at an early stage. Inadequate anticoagulation therapy with warfarin might accelerate thrombus formation in LAA; thus, INR should be maintained at a level of 2 or more within the Japanese guidelines, and appropriate and timely treatment according to age should be provided.

Study limitations

Since this was a retrospective, single-center study, the number of patients was relatively small.
Hence, care must be exercised in interpreting the results. Since the number of cases with a CHA₂DS²-VASc score >4 was very small in this study, we treated those with a CHA₂DS²-VASc score of 4–9 as one category. Therefore, we were not able to estimate the trend of the thrombus prevalence precisely for every score. To establish appropriate management using anticoagulants, it is vital to recruit a larger number of AF patients who receive care in multiple facilities and to accumulate more data for the prediction of thrombus formation based on CHA₂DS²-VASc scores.

Conclusion

The prevalence of LAA thrombus is likely to be greater in patients who have higher CHA₂DS²-VASc scores. Patients with persistent/chronic AF show a significantly higher prevalence of LAA thrombus than those with paroxysmal AF. Multivariate analysis indicated that persistent/chronic AF, higher CHA₂DS²-VASc scores, and CHF had a strong association with LAA thrombus formation in patients with NVAF who were not fully anticoagulated with warfarin.

References


Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the European Heart Rhythm Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. Europace 2007; 9: 335–379.


