Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation


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Aims There is little knowledge about the predictors of left atrial appendage (LAA) thrombi in non-valvular atrial fibrillation (NVAF). We investigated the ability of d-dimer to predict LAA thrombi.

Methods and results In this study, 925 patients with NVAF were enrolled. At the time of transoesophageal echocardiography (TEE), d-dimer levels were measured simultaneously. Significant independent predictors of LAA thrombi were the presence of congestive heart failure [odds ratio (OR) 3.10, 95% confidence interval (CI) 1.77–5.50, \( P < 0.0001 \)], a history of recent embolic events (OR 3.39, 95% CI 1.90–6.04, \( P < 0.0001 \)), and d-dimer levels (OR 97.6, 95% CI 17.3–595.8, \( P < 0.0001 \)). Receiver operating characteristic analysis yielded an optimal cutoff value of 1.15 mg/mL for d-dimer to detect LAA thrombi. LAA thrombi were detected in 21.8% of patients with higher d-dimer values, whereas it was detected in only 3.1% of patients with lower d-dimer values. d-dimer cutoff level of 1.15 mg/mL had a negative predictive value of 97% for identifying LAA thrombi.

Conclusion In patients with NVAF, d-dimer may be helpful for predicting the absence of LAA thrombi. d-dimer level was clinically useful to guide the management of patients with NVAF, especially for those complicated with congestive heart failure and/or recent embolic events.

KEYWORDS
Atrial fibrillation; Thrombus; Heart failure; Stroke

Introduction
Atrial fibrillation, the most common sustained cardiac rhythm disturbance, increases in prevalence as the population ages. Em
colic stroke is one of the most feared complications of atrial fibrillation. Compared with patients with sinus rhythm, those with atrial fibrillation have a four- to five-fold increased risk of ischaemic stroke. Transoesophageal echocardiography (TEE) allows thrombi in the left atrial appendage (LAA) to be detected with a high degree of accuracy. There is no laboratory test to aid the diagnosis of LAA thrombi. d-dimers appear to be a useful parameter for assessing the degrees of hypercoagulability. Therefore, it may have a potential role as a non-invasive marker of the presence of thrombi and risk for thrombo-embolism. In the investigation and management of deep venous thrombosis, pulmonary embolism, and acute aortic dissection, the use of d-dimer is well established. A recent study with a small number of patients shows that d-dimer is a reliable parameter to exclude the presence of atrial thrombi in patients with atrial fibrillation. We investigated the ability of d-dimer to predict LAA thrombi in several clinical situations.

Methods
Study population
Between February 1992 and February 2005, 1200 consecutive patients with non-valvular atrial fibrillation (NVAF) were eligible. The definition and classification of atrial fibrillation used in this study were based on published guidelines from the American College of Cardiology–American Heart Association and the European Society of Cardiology. At the time of TEE, plasma d-dimer level was measured simultaneously. Excluded were patients with organic valvular heart diseases, presence of prosthetic valve, aortic aneurysm, left ventricular thrombus, aortic dissection, deep vein thrombosis, and pulmonary embolism. All patients were assessed by a nine-item prediction rule to preliminarily categorize their pretest probability of deep vein thrombosis. If patients were categorized as ‘high pretest probability’, we examined deep vein thrombosis using venous ultrasonography or enhanced computed tomography. Informed consent was obtained from all patients after explanation of the study, and the study was approved by the institutional Ethics Committee.

Ultrasound evaluation
All patients underwent transthoracic echocardiography and TEE. A Philips medical ultrasonograph (Model SONOS 2500 or SONOS 5500, Philips Medical Systems, MA, USA) with a 2.5 MHz transducer and a...
5 MHz omniplane probe was used to obtain transthoracic echocardiogram and TEE. Before TEE study, the procedure was explained in greater detail, and written informed consent was obtained. Lido- 
caine hydrochloride spray was routinely used for local anaesthesia, which should cover the posterior pharynx and tongue. We used 5–10 mg diazepam intravenously for sedation, if necessary. Sedative was used for ~30% of our patients. We usually performed TEE within 15 min. The failure rate of TEE was <1% (10 patients, owing to the failure of oesophageal intubation). A careful survey of the entire atria, including the appendages, was performed by TEE. Maximal LAA areas were measured by tracing a line from the top of the upper pulmonary vein limbus along the entire endocardial LAA border. Left atrial cavity and LAA were closely inspected for the presence of thrombi, and spontaneous echo contrast (SEC) was graded from 0 to 4 following the classification of Fakkin et al.1 The LAA-emptying peak flow velocity signals within each R-R interval were averaged over a minimum of eight cardiac cycles. LAA thrombi were recognized by identifying a mobile or sessile, irregularly shaped, grey, textured density that was clearly separate from the lining of the atrial appendage. It was a clearly defined echo-dense intracavitary mass, which was acoustically distinct from the endocardium. Echocardiographers were blinded to D-dimer levels. In patients with paroxysmal atrial fibrillation (PAF), TEE was performed before they recovered to normal sinus rhythm. All TEE data were analysed by two independent cardiologists. When the results were different between the two cardiologists, a final decision was made by consensus. The interobserver intraclass correlation coefficient for the detection of thrombi was 0.99 [95% confidence interval (CI) 0.98–0.99], and that for the evaluation of SEC grade by TEE was 0.97 (95% CI 0.96–0.98). The intraobserver intraclass correlation coefficient for the detection of thrombi was 0.99 (95% CI 0.98–0.99), and that for the evaluation of SEC grade by TEE was 0.99 (95% CI 0.98–0.99).

Results

Patients population

We identified 925 patients (68.8 ± 10.3 years) with NVAF (including 250 patients with PAF, 84 with persistent atrial fibrillation, and 591 with permanent atrial fibrillation). Among these patients, 583 patients (63.0%) had hypertension, 208 (22.5%) had congestive heart failure defined as New York Heart Association (NYHA) class II or higher, and 208 (22.5%) had recent embolic events that occurred within 2 weeks (including acute ischaemic stroke); 158 patients had cerebral embolic events which were classified as cerebrovascular attack in 103 and transient ischaemic attack in 55, and 50 patients had peripheral (n=21), mesenteric artery (n=11), splenic artery (n=4), coronary artery (n=4), or renal artery (n=10) embolism.

Left atrial appendage thrombi

Eighty patients had thrombi in LAA, and only three had them in the left atrial cavity. The clinical and echocardiographic characteristics of patients with and without LAA thrombi are shown in Table 1. Patients with LAA thrombi were older and had greater prevalence of hypertensive diseases than those without LAA thrombi. Compared with patients without LAA thrombi, those with thrombi had larger left atrial dimension, lower ejection fraction, greater prevalence of moderate-to-severe SEC, and lower LAA velocities.

Multivariable analysis

On the basis of the results of univariate analysis, the following variables were entered into the multivariable model: age,

| Table 1 Baseline characteristics among patients with and without left atrial appendage thrombi |
|----------------|----------------|-------------|
| LAA thrombi (−) | LAA thrombi (+) | P-value |
| Age | 68.5 ± 10.3 | 72.0 ± 9.9 | <0.01 |
| Male (%) | 68 | 61 | 0.20 |
| Diabetes mellitus (%) | 20 | 20 | 0.93 |
| Hypertension (%) | 62 | 73 | 0.04 |
| Hyperlipidaemia (%) | 33 | 36 | 0.83 |
| LAD (mm) | 43.5 ± 6.9 | 46.6 ± 9.3 | 0.0006 |
| LVDd (mm) | 47.7 ± 10.6 | 49.2 ± 7.6 | 0.22 |
| Ejection fraction (%) | 60.9 ± 12.3 | 53.9 ± 16.1 | 0.0001 |
| LAA area (cm²) | 6.3 ± 2.9 | 7.0 ± 2.6 | 0.082 |
| LAA velocity (cm/s) | 38.5 ± 23.6 | 21.2 ± 12.4 | <0.0001 |
| Moderate SEC in LA (%) | ≥50 | 83 | <0.0001 |
| Moderate SEC in Ao (%) | ≥50 | 83 | <0.0001 |
| Ao atheroma ≥3 mm (%) | 21 | 25 | 0.46 |
| Recent embolic events (%) | 20 | 51 | <0.0001 |
| Heart failure (%) | 27 | 48 | 0.0004 |
| Adequate anticoagulation therapy (%) | 8 | 2 | <0.0001 |

LAD, left atrial dimension; LVDd, left ventricular dimension in end-diastole; LAA, left atrial appendage; SEC, spontaneous echo contrast; LA, left atrial; Ao, aorta.

Continuous variables were compared by unpaired t-test. Discrete variables were compared by χ² test with Yates’ correction. Univariate logistic regression analysis was used to assess the association of clinical and laboratory variables with the presence of LAA thrombi. Stepwise multivariable logistic regression analysis was then applied to individuate the variables independently associated with the presence of LAA thrombi. Only variables with a value of P < 0.05 on univariate analysis were included in the multivariable model. Values of P < 0.05 were considered to be statistically significant.
presence of hypertension, non-PAF, presence of congestive heart failure, a history of recent embolic events, and D-dimer levels. Independent predictors of LAA thrombi are summarized in Table 2. Multivariable analysis revealed that non-PAF, presence of congestive heart failure, a history of recent embolic events, and D-dimer levels were the independent predictors of LAA thrombi. The most powerful predictor was plasma D-dimer levels.

**Plasma D-dimer level**

Plasma D-dimer levels were significantly higher in patients with LAA thrombi than in those without thrombi (median of 2.33 and interquartile range of 1.15–6.30 vs. median of 0.59 and interquartile range of 0.35–1.22, \( P < 0.0001 \)). Distribution of D-dimer level is shown in Figure 1. ROC analysis yielded an optimal cutoff value of 1.15 \( \mu \text{g/mL} \) for D-dimers to detect the LAA thrombi (Figure 2). LAA thrombi were detected in 21.8% of patients whose plasma D-dimer levels were not <1.15 \( \mu \text{g/mL} \) \((n = 289)\) (patients with higher D-dimer levels), whereas in only 3.1% of patients, plasma D-dimer levels were <1.15 \( \mu \text{g/mL} \) \((n = 636)\). Although the plasma D-dimer cutoff value of 1.15 \( \mu \text{g/mL} \) had a sensitivity of 76% (95% CI 65–85), a specificity of 73% (95% CI 70–76), and a positive predictive value of 22% (95% CI 17–27) for identifying thrombi in LAA, it had a negative predictive value of 97% (95% CI 95–98). Patients with higher plasma D-dimer levels were older (73.2 ± 9.4 years vs. 66.8 ± 10.1 years, \( P < 0.05 \)) and had a greater prevalence of hypertensive heart diseases (71 vs. 59%, \( P < 0.05 \)) than those with lower plasma D-dimer levels. The average of the peak LAA velocities in patients with higher plasma D-dimer levels was significantly lower than that in those with lower plasma D-dimer levels (33.8 ± 21.1 vs. 38.5 ± 24.2 cm/s, \( P < 0.05 \)). Increasing grades of left atrial SEC were associated with increasing D-dimer levels (Figure 3).

**Paroxysmal atrial fibrillation**

Twelve (5%) out of 250 patients with PAF and 71 (11%) out of 675 patients without PAF had thrombi in LAA. The clinical and echocardiographic characteristics of patients with and without PAF are shown in Table 3. Patients with PAF had smaller left atrial dimension, smaller left ventricular dimension in the end-diastole, higher ejection fraction, less prevalence of moderate-to-severe SEC, higher LAA velocities, and smaller LAA area than those without PAF. In patients with PAF, although the plasma D-dimer cutoff value of 1.15 \( \mu \text{g/mL} \) had a sensitivity of 75% (95% CI 47–91), a specificity of 70% (95% CI 64–76), and a positive predictive value of 11% (95% CI 5–20) for identifying thrombi in LAA, it had a negative predictive value of 98% (95% CI 95–100). In patients without PAF, although the plasma D-dimer cutoff value of 1.15 \( \mu \text{g/mL} \) had a sensitivity of 76% (95% CI 64–85), a specificity of 74% (95% CI 71–78), and a positive predictive value of 26% (95% CI 20–32) for identifying thrombi in LAA, it had a negative predictive value of 96% (95% CI 94–98).

**Patients’ complications and left atrial appendage thrombi**

Among patients complicated with congestive heart failure \((n = 208)\), 33 (15.9%) had LAA thrombi. Although the plasma D-dimer cutoff value of 1.15 \( \mu \text{g/mL} \) had a specificity of 66% (95% CI 59–73) and a positive predictive value of 32% (95% CI 23–43) for identifying thrombi in LAA, it had a sensitivity of 85% (95% CI 68–95) and a negative predictive value of 96% (95% CI 91–98).

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**Table 2** Results of the multivariable analysis: independent predictors of left atrial thrombi

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-paroxysmal atrial fibrillation</td>
<td>2.13</td>
<td>1.15–4.19</td>
<td>0.02</td>
</tr>
<tr>
<td>Presence of congestive heart failure</td>
<td>3.10</td>
<td>1.77–5.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A history of recent embolic events</td>
<td>3.39</td>
<td>1.90–6.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>D-dimer levels</td>
<td>97.6</td>
<td>17.3–595.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Among patients complicated with recent embolic events (n = 208), 42 (20.2%) had LAA thrombi. Patients with recent embolic events appeared to have higher D-dimer levels (median of 2.85 and interquartile range of 1.06–7.85 vs. median of 0.83 and interquartile range of 0.45–2.10, P < 0.0001). The plasma D-dimer cutoff value of 1.15 μg/mL had a sensitivity of 91% (95% CI 77–97) and a negative predictive value of 97% (95% CI 91–99), although it had a specificity of 67% (95% CI 62–72) and a positive predictive value of 35% (95% CI 28–43) for identifying thrombi in LAA, and it had a sensitivity of 89% (95% CI 79–95) and a negative predictive value of 97% (95% CI 94–99).

**Anticoagulant therapy**

Seventy-three patients received an adequate anticoagulation therapy (international normalized ratios ≥ 2.0). LAA thrombi were detected in only two patients (2.7%) receiving the adequate anticoagulation therapy. These two patients had higher D-dimer levels (≥1.15 μg/mL).

**Discussion**

D-dimer levels and left atrial appendage thrombi

This study demonstrated the ability of D-dimer to predict LAA thrombi in NVAF. D-dimer has gained widespread clinical use as a parameter for the detection of fibrin formation. Previous studies demonstrate that patients with atrial fibrillation show significant increases in plasma fibrinogen and D-dimer level, suggesting the presence of a hypercoagulable or pro-thrombotic state. Our data clearly showed that, in patients with atrial fibrillation, the use of a single laboratory test could exclude the possibility of LAA thrombi formation. The negative predictive value of D-dimer measurement with a cutoff of 1.15 μg/mL in our study corresponded to the 98% rate reported by Somloi et al. However, D-dimer concentration of not less than 1.15 μg/mL could not be used for positive diagnosis because the false-positive rate was 27% (positive predictive value of 22%). Several disease conditions such as infectious or inflammatory diseases and cancer were associated with fibrin formation and degradation. In a population with D-dimer concentration of not less than 1.15 μg/mL, patients with these conditions could potentially be included. Although false-positive results (27%) and false-negative results (24%) were relatively often observed, we thought it was important for patients with atrial fibrillation to do risk stratification. We should perform the immediate and adequate anticoagulant therapy and careful observation for patients with LAA thrombi to prevent serious sequela. From this point of view, we thought our results are useful for risk stratification. We believed our results might lead to prompt detection of LAA thrombi and prevention of serious sequela.

Most thrombi in NVAF originate in LAA, suggesting the origin of thrombo-embolism. A case of a disappearing LAA thrombus resulting in a stroke is reported. Therefore, we thought it was important to detect LAA thrombi before they were embolized. Among the patients other than those with recent embolic events, 41 (5.7%) had LAA thrombi in our study. The immediate treatments with adequate anticoagulant therapy and preventive percutaneous or surgical intervention should be performed, if needed. Several randomized, prospective trials involving patients with NVAF have confirmed a significant reduction in the risk of stroke with warfarin. These trials have provided a basis of important guidelines for the use of warfarin in such patients.
increased risk of stroke in patients with atrial fibrillation may also warrant the institution of anticoagulant therapy. Three recent randomized studies\textsuperscript{22-24} suggest that the strategy used to treat atrial fibrillation (rate control vs. rhythm control) does not have a substantial effect on the quality of life or cardiovascular endpoints. However, in highly symptomatic patients whose heart rate cannot be controlled, rhythm control may still be preferable. When cardioversion was being considered, determination of absence of LAA thrombi by d-dimer might be utilized.

Optimal cutoff level

In this study, we identified the ‘optimal’ cutoff by using ROC analysis. The best cutoff has the highest sensitivity and lowest 1-specificity and is therefore located as high up on the vertical axis and as far left on the horizontal axis as possible (upper left corner). When investigating whether d-dimer can be used to eliminate the possibility of LAA thrombi formation in patients with NVAF, a decision-maker should choose a cutoff criterion from the higher right-hand portion of the ROC curve to minimize false negatives. We compared a cutoff level of 1.15 µg/mL (closest to the left upper corner of the ROC curve) with that of 0.80 µg/mL (higher right-hand portion of the ROC curve). At a cutoff level of 0.80 µg/mL, the sensitivity was 81.9% (95% CI 72–90), specificity 62.1% (95% CI 59–65), positive predictive value 17.6% (95% CI 14–22), and negative predictive value 97.2% (95% CI 95–98) for identifying thrombi in LAA. At a cutoff level of 1.15 µg/mL, the sensitivity was 75.9% (95% CI 65–85), specificity 73.1% (95% CI 70–76), positive predictive value 21.7% (95% CI 17–27), and negative predictive value 97.0% (95% CI 95–98) for identifying thrombi in LAA. We established the ‘optimal’ cutoff level as 1.15 µg/mL because a negative predictive value was almost the same between cutoff levels of 1.15 and 0.80 µg/mL.

We evaluated the possibility of LAA thrombi formation by dichotomized d-dimer levels after confirming the ability of d-dimer to predict LAA thrombi in patients with NVAF. In clinical settings, this categorization has been useful for risk stratification of patients with atrial fibrillation. However, there is uncertainty about the ‘optimal’ cutoff level in patient populations other than those with atrial fibrillation because the cutoff levels are known to be very susceptible to changes in individual populations.

\textit{d-dimer levels and left atrial spontaneous echo contrast}

Left atrial SEC may provide visual demonstration of blood stasis within the left atrial cavity. A high prevalence of left atrial SEC has been found in patients with LAA thrombi.\textsuperscript{25} The presence of SEC in the left atrium has been proposed as a marker of increased thrombo-embolic risk. Our study elucidated an increase in d-dimer levels with grades of left atrial SEC. A more or less compensated hypercoagulable state exists in many patients with atrial fibrillation. Measurement of d-dimer level was a means for the detection of LAA thrombi and the hypercoagulable state in our population. However, there are few prospective data that describe the degree of predictability provided by hypercoagulability for the risk of having thrombo-embolic diseases.

\textbf{Congestive heart failure and recent embolic events}

Recent congestive heart failure, a history of hypertension, and previous arterial thrombo-embolism are significantly and independently associated with a substantial risk of thrombo-embolism.\textsuperscript{26} Multivariable analysis of selected clinical variables showed that non-PAF, presence of congestive heart failure, a history of recent embolic events, and d-dimer levels were associated with a significantly increased risk of LAA thrombi that might reflect the incidence of thrombo-embolic events. In our study, by the measurement of d-dimer levels, LAA thrombi could be sensitively detected in patients with NVAF complicated with congestive heart failure and/or recent embolic events.

\textbf{Limitations}

First, in this study, d-dimer was measured by LPIA, and data and conclusions could be drawn for this specific d-dimer assay only. d-dimer assay included LPIA, manual latex agglutination assays, sandwich-type enzyme-linked immunoassays (ELISA), automated ELISA systems, and membrane-based immunofiltration assay systems. According to the results of a FACT study,\textsuperscript{27} however, d-dimer LPIA displays a response similar to that in most of the other assays. Second, antithrombotic therapies were not randomized. The majority of patients were not anticoagulated. Thirdly, our results of patients complicated with a history of recent embolic events were likely to underestimate the number of patients with LAA thrombi because LAA thrombi had already been embolized when we performed TEE.

\textbf{Conclusions}

In a selected cohort of patients with NVAF, d-dimer may be helpful for predicting the absence of LAA thrombi owing to its high negative predictive value. d-dimer level was clinically useful to guide the management of patients with NVAF, especially for those complicated with congestive heart failure and/or recent embolic events.

\textbf{Conflict of interest:} none declared.

\textbf{References}


