Impact of off-label under-dose direct oral anticoagulant on coagulation and fibrinolytic markers in patients with atrial fibrillation

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Research Article

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Abstract

Objectives: Direct oral anticoagulants (DOAC) have been approved for oral anticoagulation in patients with non-valvular atrial fibrillation (AF). On the other hand, DOAC are sometimes prescribed off-label under-doses for patients with AF. This study aimed to compare the effects of different DOAC doses on coagulation and fibrinolytic markers.

Methods: A total of 88 patients with AF (age, 68 ± 11 years; male sex, 45%; persistent AF, 43%) were analyzed. All patients received edoxaban (60 or 30 mg) once daily. For this study, patients were divided into three groups according to whether they had been treated before the ablation procedure under an appropriate standard-dose group (n = 30 [34.1%]), appropriate low-dose group (n = 35 [39.8%]), or off-label under-dose group (n = 23 [26.1%]). Coagulation and fibrinolytic markers and echocardiographic parameters were examined before ablation.

Results: There were no significant baseline differences in AF type, plasma B-type natriuretic peptide, protein C, fibrinogen, D-dimer level, left ventricular ejection fraction, or left atrial dimension among the three groups. The prothrombin fragment 1+2 (F1+2) level was significantly different among the appropriate standard-dose, appropriate low-dose, and off-label under-dose groups (105.9 ± 29.4, 142.6 ± 41.3, and 142.8 ± 84.9 pmol/L, respectively; P = 0.011). After multivariate analysis, the F1+2 was significantly higher in the off-label low-dose group than in the standard-dose group when compared among the three groups (P = 0.034, Bonferroni test).

Conclusion: Our results suggest that an appropriate standard dose of edoxaban is required to suppress hypercoagulability in patients with AF.

Highlights

- Atrial fibrillation (AF) increases the risk of cerebral and systemic embolism. Direct oral anticoagulant (DOAC) therapy is the cornerstone of thromboembolic stroke prevention in patients with AF.
- In clinical practice, physicians improperly reduce DOAC doses to reduce the risk of bleeding even though they are aware of the standard dosing regimen criteria. Off-label under-doses are most commonly prescribed for older patients, as well as for those with low body weight and low renal function.
- Patients in this study were divided into three groups according to whether they had been treated before the ablation procedure under an appropriate standard-dose group (n = 30 [34.1%]), appropriate low-dose group (n = 35 [39.8%]), or off-label under-dose group (n = 23 [26.1%]). Age, creatinine clearance, and CHADS2-VASc score were significantly different among the three groups.
- There were no significant differences in AF type, history of stroke/transient ischemic attack, plasma B-type natriuretic peptide, protein C, fibrinogen, D-dimer level, left ventricular ejection fraction, or left atrial dimension among the three groups.
- After multivariate analysis, the F1+2 was significantly higher in the off-label low dose group than in the standard dose group when compared among the three groups (P = 0.034).

Introduction
Atrial brillation (AF) increases the risk of cerebral and systemic embolism. In addition to vitamin K antagonists, direct oral anticoagulants (DOAC) have been approved as oral anticoagulants in patients with non-valvular AF (NVAF), following the results of large clinical trials [1–4].

Recent clinical-based studies of DOAC treatment have identified off-label DOAC as being associated with an increased risk of adverse events in patients with NVAF [5, 6]. However, DOAC dosing is nuanced and different for each agent and indication, causing dosing errors to occur frequently in the general population [7]. In clinical practice, physicians improperly reduce DOAC doses to reduce the risk of bleeding even though they are aware of the standard dosing regimen criteria. On the other hand, catheter ablation is an established treatment for symptomatic AF. Guidelines have incorporated catheter ablation of symptomatic AF as a class I or II indication, depending on previous antiarrhythmic treatment and the type of AF [8–10]. Although AF ablation is an established treatment, there are some complications, such as perioperative stroke, bleeding events, and cardiac tamponade [11]. Because of periprocedural bleeding complications, such as cardiac tamponade, physicians inappropriately reduce the dose of any DOAC, despite knowledge of the criteria for a standard-dose regimen, in an attempt to lower the risk of bleeding. Off-label under-doses are most commonly prescribed for older patients, as well as for those with low body weight and low renal function [5, 12].

The prothrombin fragment 1 + 2 (F1 + 2) is cleaved from the amino-terminal end of human prothrombin when zymogen is activated by factor Xa to produce thrombin. Prothrombin activation, as measured by the F1 + 2 assay, is reportedly suppressed by oral anticoagulants in the blood of patients with thrombotic diatheses [13]. Since increased plasma levels of F1 + 2 are reflected in thrombin generation, the measurement of F1 + 2 level is considered to be useful for evaluating the high risk of thrombosis.

This study aimed to compare the effects of different DOAC doses on coagulation and fibrinolytic markers.

**Methods**

**Study design and study population**

This single-center, prospective, non-randomized study aimed to identify the anticoagulant effects of edoxaban 60 mg/day (standard-dose), 30 mg/day for patients with creatinine clearance ≤ 50 mL/min or body weight ≤ 60 kg (low-dose), and 30 mg/day for patients with creatinine clearance > 50 mL/min and body weight > 60 kg (under-dose) in AF patients. We enrolled consecutive patients with AF aged > 20 years who underwent ablation at the Yao Municipal Hospital between February 2018 and July 2019. After ablation, all patients were followed up for 12 months to observe the presence or absence of bleeding or thromboembolic events. All patients underwent anticoagulation therapy with edoxaban ≥ 4 weeks before the procedure (edoxaban 60 mg or 30 mg q.d.). The exclusion criteria were as follows: a history of severe valvular heart disease, acute heart failure, thromboembolism, electrical defibrillation, trauma, and infection within 3 months before ablation. All patients underwent baseline transthoracic echocardiography (TTE) within 1 week and transesophageal echocardiography (TEE) before the ablation procedure. Baseline demographic and clinical information were obtained, and laboratory examinations were performed before catheter ablation. Anticoagulants were discontinued only on the day of ablation.
Written informed consent was obtained from all the patients before participation, and the study protocol was approved by the Institutional Ethics Committee.

Peripheral venous blood samples were collected on the morning of the ablation day. TTE was performed within a week before catheter ablation using a Philips Sonos 7500 ultrasound instrument (Philips Healthcare, Amsterdam, The Netherlands) equipped with a sector transducer (carrier frequency, 2.5 or 3.75 MHz). A 5-MHz phased-array multiplane probe was used for the TEE. TTE parameters at baseline included the left ventricular diastolic dimension (LVDd), ejection fraction (EF), left atrial diameter (LAD), left atrial volume index (LAVI), and E/e' ratio. Baseline TEE parameters included left atrial appendage (LAA) peak emptying velocity and presence of spontaneous echo contrast (SEC).

The following plasma or serum biomarkers were analyzed centrally at baseline: (1) thrombogenesis/fibrinolysis biomarkers, D-dimer, F1 + 2, protein C, and thrombomodulin; and (2) inflammation biomarker, C-reactive protein (CRP). The association between demographic data and medical history with biomarker levels was investigated at baseline. In addition, we assessed the relationship between DOAC dose, biomarker level, and echocardiographic characteristics.

**Statistical analysis**

Data are expressed as mean and standard deviation or median with 25th to 75th percentiles for normally distributed and skewed variables, respectively. Normality was assessed using the Shapiro-Wilk test. We used t-test and chi-squared test to compare the continuous and categorical variables, respectively. Between-group differences in continuous variables were evaluated using one-way analysis of variance, and between group differences in categorical variables were analyzed using the chi-square test. The multiplicity of the tests was corrected using the Bonferroni’s method. Statistical significance was set at P value < 0.05. Statistical analyses were performed using IBM SPSS (version 26.0, SPSS, Inc., Chicago, Illinois, USA).

**Results**

During the entry period, 98 patients with AF were initially screened, and 88 patients (age, 68 ± 11 years; male sex, 45%; paroxysmal AF, n = 49, persistent AF, n = 39) were analyzed. Patients in this study were divided into three groups according to whether they had been treated before the ablation procedure under an appropriate standard-dose group (n = 30 [34.1%]), appropriate low-dose group (n = 35 [39.8%]), or off-label under-dose group (n = 23 [26.1%]) (Fig. 1). Age, creatinine clearance, and CHADS2-VASc score were significantly different among the three groups (P < 0.001; Table 1). There were no significant baseline differences in AF type, history of stroke/transient ischemic attack (TIA), plasma B-type natriuretic peptide, protein C, fibrinogen, D-dimer level, LVEF, or LAD among the three groups. However, the F1 + 2 level was significantly different between the groups (P = 0.017, Table 1). After adjustment for potential confounders (sex, body weight), only F1 + 2 among the coagulation/fibrinolytic factors showed a significant difference among the three groups (P = 0.027, Table 2).
Table 1
Comparison of baseline characteristics among patients on standard-dose, low-dose, and under-dose.

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 88)</th>
<th>Standard dose (n = 30)</th>
<th>Low dose (n = 35)</th>
<th>Under dose (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>46 (52)</td>
<td>25 (83)</td>
<td>6 (17)</td>
<td>15 (65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>68.2 ± 10.9</td>
<td>59.1 ± 10.3</td>
<td>73.2 ± 8.6</td>
<td>72.6 ± 6.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>64.0 ± 13.0</td>
<td>73.2 ± 10.6</td>
<td>51.9 ± 6.5</td>
<td>70.3 ± 7.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AF type, persistent AF (%)</td>
<td>38 (43)</td>
<td>10 (33)</td>
<td>15 (43)</td>
<td>13 (57)</td>
<td>0.353</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>17 (19)</td>
<td>3 (10)</td>
<td>10 (29)</td>
<td>4 (17)</td>
<td>0.165</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>50 (57)</td>
<td>11 (37)</td>
<td>23 (66)</td>
<td>16 (70)</td>
<td>0.041</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>9 (10)</td>
<td>3 (10)</td>
<td>4 (11)</td>
<td>2 (9)</td>
<td>0.946</td>
</tr>
<tr>
<td>Stroke, TIA (%)</td>
<td>4 (5)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>1 (4)</td>
<td>0.76</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>1.4 ± 1.0</td>
<td>0.8 ± 0.9</td>
<td>1.7 ± 1.1</td>
<td>1.5 ± 0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>CHADS2-VASc score</td>
<td>2.5 ± 1.5</td>
<td>1.2 ± 1.2</td>
<td>3.4 ± 1.2</td>
<td>2.8 ± 1.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACEi/ARB (%)</td>
<td>27 (31)</td>
<td>6 (2)</td>
<td>11 (31)</td>
<td>10 (43)</td>
<td>0.188</td>
</tr>
<tr>
<td>β-blocker (%)</td>
<td>34 (39)</td>
<td>10 (33)</td>
<td>14 (40)</td>
<td>10 (33)</td>
<td>0.744</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>17 (19)</td>
<td>3 (10)</td>
<td>10 (29)</td>
<td>4 (17)</td>
<td>0.165</td>
</tr>
<tr>
<td>CLCr, mL/min</td>
<td>76.7 ± 31.5</td>
<td>101.1 ± 38.4</td>
<td>58.0 ± 15.7</td>
<td>73.2 ± 14.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>13.9 ± 1.7</td>
<td>14.8 ± 1.8</td>
<td>13.1 ± 1.3</td>
<td>13.8 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>157.6 ± 164.6</td>
<td>113.7 ± 159.1</td>
<td>193.4 ± 177.2</td>
<td>160.4 ± 143.1</td>
<td>0.15</td>
</tr>
<tr>
<td>D-dimer, µg/mL</td>
<td>0.53 ± 0.31</td>
<td>0.49 ± 0.34</td>
<td>0.57 ± 0.31</td>
<td>0.53 ± 0.28</td>
<td>0.651</td>
</tr>
<tr>
<td>CRP systemic, mg/dL</td>
<td>0.18 ± 0.28</td>
<td>0.20 ± 0.28</td>
<td>0.15 ± 0.24</td>
<td>0.21 ± 0.35</td>
<td>0.643</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>273.7 ± 52.7</td>
<td>261.4 ± 57.5</td>
<td>282.1 ± 50.3</td>
<td>277.0 ± 48.9</td>
<td>0.272</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or numbers (percentage).

AF, atrial fibrillation; TIA, transient ischemic attack; CLCr, creatinine clearance; Hb, hemoglobin; BNP, brain natriuretic peptide; CRP, C-reactive protein; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LAVI, left atrial volume index; LAA, left atrial appendage; SEC, spontaneous echo contrast
<table>
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<tr>
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<th>Total (n = 88)</th>
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<th>Low dose (n = 35)</th>
<th>Under dose (n = 23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin fragment 1 + 2, pmol/L</td>
<td>128.6 ± 54.6</td>
<td>105.9 ± 29.4</td>
<td>138.9 ± 39.2</td>
<td>142.8 ± 84.9</td>
<td>0.017</td>
</tr>
<tr>
<td>Protein C, %</td>
<td>97.0 ± 19.7</td>
<td>96.5 ± 22.2</td>
<td>96.7 ± 18.2</td>
<td>98.0 ± 19.1</td>
<td>0.959</td>
</tr>
<tr>
<td>Thrombomodulin, ng/mL</td>
<td>2.4 ± 0.8</td>
<td>2.4 ± 0.6</td>
<td>2.4 ± 0.8</td>
<td>2.5 ± 0.8</td>
<td>0.669</td>
</tr>
<tr>
<td>LVDd, mm</td>
<td>45.8 ± 5.4</td>
<td>48.7 ± 4.6</td>
<td>43.7 ± 5.1</td>
<td>45.2 ± 5.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVDs, mm</td>
<td>29.9 ± 5.8</td>
<td>31.9 ± 5.6</td>
<td>28.2 ± 5.5</td>
<td>29.8 ± 5.9</td>
<td>0.037</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>63.5 ± 10.0</td>
<td>62.8 ± 10.1</td>
<td>64.5 ± 9.4</td>
<td>62.8 ± 10.9</td>
<td>0.737</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>41.9 ± 7.0</td>
<td>41.6 ± 7.4</td>
<td>40.4 ± 6.9</td>
<td>44.4 ± 6.0</td>
<td>0.108</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>39.7 ± 16.8</td>
<td>37.2 ± 18.4</td>
<td>41.3 ± 16.9</td>
<td>40.7 ± 14.6</td>
<td>0.594</td>
</tr>
<tr>
<td>E/e'</td>
<td>8.9 ± 2.4</td>
<td>7.4 ± 1.4</td>
<td>10.0 ± 2.6</td>
<td>9.3 ± 2.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LAA flow velocity, cm/s</td>
<td>39.8 ± 24.3</td>
<td>43.3 ± 17.7</td>
<td>38.4 ± 24.0</td>
<td>32.8 ± 21.5</td>
<td>0.065</td>
</tr>
<tr>
<td>SEC (+), n (%)</td>
<td>15 (17)</td>
<td>5 (17)</td>
<td>7 (20)</td>
<td>3 (13)</td>
<td>0.664</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or numbers (percentage).

AF, atrial fibrillation; TIA, transient ischemic attack; CLCr, creatinine clearance; Hb, hemoglobin; BNP, brain natriuretic peptide; CRP, C-reactive protein; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LAVI, left atrial volume index; LAA, left atrial appendage; SEC, spontaneous echo contrast
Table 2
Differences in the coagulation or fibrinolytic factors after adjustment for potential confounders.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Standard dose</th>
<th>Low dose</th>
<th>Under dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Modifide Average</td>
<td>Standard Error</td>
<td>Modifide Average</td>
</tr>
<tr>
<td>D-dimer, µg/mL</td>
<td>0.50</td>
<td>0.07</td>
<td>0.56</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>266.90</td>
<td>11.83</td>
<td>276.99</td>
</tr>
<tr>
<td>Prothrombin fragment 1 + 2, pmol/L</td>
<td>102.22</td>
<td>11.96</td>
<td>142.62</td>
</tr>
<tr>
<td>Protein C, %</td>
<td>93.01</td>
<td>4.33</td>
<td>102.22</td>
</tr>
<tr>
<td>Thrombomodulin, ng/mL</td>
<td>2.23</td>
<td>0.16</td>
<td>2.55</td>
</tr>
</tbody>
</table>

Covariate: sex, body weight * P < 0.05

After multivariate analysis, the F1 + 2 was significantly higher in the off-label low-dose group than in the standard-dose group when compared among the three groups (P = 0.034) (Fig. 2, Supplementary Table 1).

During the 12-month follow-up period after ablation, one patient in the off-label low-dose group had a TIA attack and one patient in the low-dose group had urinary tract bleeding.

Discussion

Our major findings were as follows: First, inappropriate low doses were found in 26.1% of patients, and age, sex, creatinine clearance, and CHADS2-VASc score were significantly different between the appropriate standard-dose, appropriate low-dose, and off-label low-dose groups. Second, D-dimer, fibrinogen, protein C, thrombomodulin, and CRP were not different among the three groups, but the F1 + 2 was significantly higher in the off-label low-dose group than in the standard-dose group when compared with the appropriate standard-dose, appropriate low-dose, and off-label low-dose groups.

In our study, off-label low-dose DOAC therapy was administered to 26.1% of the patients given a DOAC before AF ablation. Age, sex, creatinine clearance, and CHADS2-VASc score were significantly different among the three groups. An analysis of data from the Fushimi AF Registry, a well-known registry of patients with AF in Japan, most of whom have not undergone ablation, revealed off-label underdosing in 29% of dabigatran users, 26% of apixaban users, and 21% of rivaroxaban users [5]. In addition, analysis of data from the SAKURA AF registry revealed underdosing in 22% of DOAC users [14]. In contrast, the U.S. Food and Drug Administration (FDA) specified that 13.3% of 13,392 patients who did not have a renal indication for dose reduction received off-label low-dose [15]. In a European registry, 18% of the patients received an off-label low-dose [16]. Inappropriate low doses are more frequent in Asia than in the Western countries because bleeding is more frequent in Asians than in non-Asians, and physicians may be inclined to avoid bleeding.
complications [17, 18]. Off-label DOAC dosing has been reported to be more common among older patients, female patients, underweight patients, and those with chronic kidney disease, and our study had similar results [19].

However, numerous investigators have reported a strong association between advanced age, prior stroke/TIA, high CHADS2 and CHA2DS2-VASc scores, and the occurrence of thromboembolic events [20, 21]. Since some risk factors for thromboembolism and bleeding are common, we need to understand the risk factors of individual patients to control thromboembolism and avoid bleeding complications.

D-dimer, fibrinogen, protein C, and thrombomodulin levels were not different among the three groups. However, F1 + 2 was significantly higher in the off-label low dose group than in the standard-dose group when compared with the appropriate standard-dose, appropriate low-dose, and off-label low-dose groups. F1 + 2 is a marker of thrombin generation and represents coagulation activity. F1 + 2 is a peptide liberated from prothrombin when it is converted to thrombin by activated factor X (FXa). It reflects thrombin production and is a coagulation activation marker [22, 23]. A previous study of patients administered DOAC therapy revealed that inappropriate underdosing was a risk factor for recurrent ischemic stroke [24]. According to the ORBIT-AF II Registry, DOAC underdosing is associated with increased cardiovascular hospitalization [6, 15]. Compared with on-label doses of DOACs, off-label under-doses are associated with increased risks of stroke, systemic embolism, and all-cause death [25]. In a report on the blood concentration of DOAC, the maximum blood concentration was significantly lower in the off-label under-dose group than in the standard dose group, but there was no significant difference between the low-dose group and the off-label under-dose group [26]. In this study, F1 + 2 levels were higher in the inappropriate low-dose group than in the appropriate standard-dose group, which may reflect a lower blood concentration of the Xa inhibitor.

Protein C and thrombomodulin exhibited anticoagulant effects. Protein C is activated by thrombin bound to thrombomodulin on the vascular endothelium and inactivates activated factor V and factor VIII by degrading them through the cofactor action of protein S, thus preventing coagulation activation [27, 28]. Thrombomodulin, a marker of vascular endothelial damage, is involved in the antithrombotic action of vascular endothelium and inhibits coagulation. Thrombomodulin traps thrombin and exerts anticoagulant activity. Thrombin trapped by thrombomodulin loses coagulation activity. In addition, the thrombin-thrombomodulin complex activates coagulation inhibitor protein C, which is converted to activated protein C [29, 30]. Edoxaban is unlikely to prolong coagulation time, which means that protein C activity is unlikely to be affected [31].

D-dimer is a molecular marker of the coagulation fibrinolysis system and is indirect evidence of the formation of crosslinked fibrin in vivo. It increases with the occurrence of various types of thrombosis. It was previously reported that plasma D-dimer levels have a high negative predictive value to rule out the presence of a thrombus [32, 33]. Fibrinogen is a glycoprotein with a molecular weight of 340 kDa, in which three polypeptides, the Aα-chain, Bβ-chain, and γ-chain, form a disulfide bond and further form a dimer. Fibrinogen is a coagulation factor that serves as the primary substrate for hemostatic plugs. This study included patients before AF ablation, and patients with intracardiac thrombus on TTE or TEE were excluded, which may have resulted in no difference in D-dimer or fibrinogen levels.
Study Limitations

The present study has several limitations. First, it was performed at a single institution with a small sample size. Second, there were differences in baseline patient characteristics. This study adjusted multiple variables between the three groups using multivariate analysis because it compared three different groups. Numerous clinical factors are involved in the occurrence of thrombosis. Thus, it was challenging to perform statistical comparisons of the clinical outcomes among the three dose groups, even if some of the clinical factors were adjusted. Third, the blood sample was measured only once before ablation and may not reflect interindividual variation. Therefore, dose reductions are needed to ascertain the risk in individual patients and further studies are required to assess whether thrombotic and bleeding events can be prevented.

Conclusion

The off-label use of DOAC is clinically encountered in patients with AF. Our results suggest that an appropriate standard dose of edoxaban is required to suppress hypercoagulability in patients with AF.

Abbreviations

AF, atrial fibrillation; CRP, C-reactive protein; DOAC, direct oral anticoagulant; CLCr, creatinine clearance; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; LA, left atrial; LAA, left atrial appendage; LAD, left atrial diameter; LAVI, left atrial volume index; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; PVI, pulmonary vein isolation; SEC, spontaneous echo contrast; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Declarations

Acknowledgements

None

Author contributions

TW conceptualized the project. SH performed quality assurance of data extraction and helped in the analysis. Others contributed to the design of the study and interpretation of the results. The manuscript was revised by the authors and the submission of the final manuscript was approved by all authors.

Funding

The authors did not receive support from any organization for the submitted work.

Data Availability

Formal requests to access the dataset need to be sent to the corresponding author (Tetsuya Watanabe).

Ethics approval and consent to participate
The study was approved by the Scientific and Research Ethics Committee of the Yao Municipal Hospital and was carried out in accordance with the tenets of the Declaration of Helsinki. Patients provided written informed consent prior to their participation in the study.

Conflict of interest

The authors have no competing interests to declare that are relevant to the content of this article.

Ethical approval

The authors state that no ethical approval was needed.

References


Figure 1

Study flow chart. PVI, pulmonary vein isolation

98 patients scheduled for PVI

10 excluded
3 electrical defibrillation
2 severe valvular heart disease
2 trauma
2 infection
1 acute heart failure

Study entry: 88 patients (men, 45%)
(appropriate standard-dose group (n = 30 [34.1%]),
appropriate low-dose group (n = 35 [39.8%])
off-label under-dose group (n = 23 [26.1%])
All patients underwent anticoagulation for least 4 weeks

Collect peripheral blood samples before PVI

12 months follow-up (88 patients)

p for ANOVA=0.017
p=0.034
p=1.000
p=0.152

(pmol/L)
200
160
120
80
40
0
standard-dose low-dose under-dose

Study fow. PVI: pulmonary vein isolation
Figure 2

Association between prothrombin fragment 1+2 and edoxaban dose

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- DOACSupplymentary.docx