Thromboembolic Events in Paroxysmal vs. Permanent Non-Valvular Atrial Fibrillation – Subanalysis of the J-RHYTHM Registry –

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Background: It is disputed whether the risk of cardiogenic embolism varies with type of atrial fibrillation (AF). Although several studies have found that the risk of cardiogenic embolism was similar among paroxysmal and persistent/permanent AF, a few studies have found that patients with paroxysmal AF had a lower rate of stroke and systemic embolism than those with persistent/permanent AF. In the present study, post-hoc analysis of the J-RHYTHM Registry was done to compare the risk of thromboembolic events among 3 types of non-valvular AF (NVAF).

Methods and Results: A total of 7,406 NVAF patients were followed up prospectively for 2 years. At baseline, warfarin was used for 78.6%, 90.0%, and 91.8% of patients with paroxysmal, persistent, and permanent AF, respectively. There were 126 thromboembolic events during the follow-up period. The crude event rate was 2-fold higher among the patients with permanent NVAF (2.29%) than among those with paroxysmal (1.16%) or persistent (1.20%) NVAF (P=0.001). After adjusting for warfarin use and CHA2DS2-VASc score components, however, the hazard ratio for thromboembolism did not differ between paroxysmal (reference) and permanent NVAF (1.007; 95% confidence interval: 0.955–1.061).

Conclusions: The crude rate of thromboembolic events was higher in permanent NVAF than in paroxysmal NVAF, but after adjusting for warfarin use and CHA2DS2-VASc score components, paroxysmal and permanent NVAF patients had similar risk of thromboembolism. (Circ J 2014; 78: 2388–2393)

Key Words: Paroxysmal atrial fibrillation; Permanent atrial fibrillation; Risk factor; Thromboembolic event

Atrial fibrillation (AF), a common form of cardiac arrhythmia, is a well known risk factor for cardiogenic embolism. It is disputed whether the risk of cardiogenic embolism varies with type of AF; that is, paroxysmal, persistent, or permanent. Several studies have found that the risk of cardiogenic embolism is similar in paroxysmal and persistent/permanent AF, but a few prospective studies have shown that anticoagulated patients with paroxysmal non-valvular AF (NVAF) have a lower rate of stroke or systemic embolic events than those with persistent/permanent NVAF. No prospective studies on this issue have been conducted in Japan. In a recent study in which more than 7,000 AF patients from the J-RHYTHM Registry were followed up prospectively for 2 years, we found that patients with paroxysmal NVAF are at significantly lower risk of thromboembolic events than those with permanent NVAF. In the latter study, many components of the CHA2DS2-VASc score (which is calculated by assigning 1 point each for congestive heart failure, hypertension, diabetes, history of vascular disease, age 65–74 years, and female sex; and 2 points each for age ≥75 years and history of stroke) were not included as explanatory variables in the multivariate analysis because the associated p-values on univariate analysis exceeded 0.25. In addition, there could be ethnic differences in the prognosis of NVAF patients. For example, thromboembolic risk is higher in female AF patients than in male AF patients in Western countries, but this is not the case for...
At enrollment, the treating physicians divided the patients into 3 groups based on type of AF (ie, paroxysmal, persistent, or permanent AF). Paroxysmal AF was defined as AF that terminated spontaneously within 7 days; persistent AF, as AF that lasted >7 days but could be terminated; and permanent AF as AF that could not be terminated. Patients who had been in sinus rhythm for more than 1 year were not included in the J-RHYTHM Registry.

Methods

The details of the study design, main analysis, and subanalyses have been reported previously. Briefly, the study protocol conformed to the Declaration of Helsinki and was approved by each of the participating institutions. Consecutive AF patients were recruited at the outpatient clinic of each institution from January 2009 to July 2009. All of the patients provided written informed consent, and all of the participating physicians were cardiologists. The anti-thrombotic drugs used and the doses were selected by the treating physicians. A total of 7,937 AF patients (mean age, 69.7 years) were enrolled. Of these, 421 patients had mitral stenosis or had undergone mechanical valve replacement; therefore, the remaining 7,516 NVAF patients were examined in the present subanalysis. The CHADS2 score (which is calculated by assigning 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes; and 2 points for a history of stroke) and the CHA2DS2-VASc score were calculated. In the present analysis, vascular disease included coronary artery disease, but not old myocardial infarction, peripheral artery disease, or aortic plaque, because information regarding the latter 3 conditions was not contained in the J-RHYTHM Registry.

At enrollment, the treating physicians divided the patients into 3 groups based on type of AF (ie, paroxysmal, persistent, or permanent AF). Paroxysmal AF was defined as AF that terminated spontaneously within 7 days; persistent AF, as AF that lasted >7 days but could be terminated; and permanent AF as AF that could not be terminated. Patients who had been in sinus rhythm for more than 1 year were not included in the J-RHYTHM Registry.

The patients were followed up for 2 years or until an end-point occurred, whichever occurred first. The thromboembolic endpoints consisted of symptomatic cerebral infarction, transient ischemic attack (TIA), or systemic embolism. Cerebral infarction and TIA were diagnosed according to the standard criteria.

Major bleeding requiring hospital admission was selected as the safety endpoint.

Statistical Analysis

Data are presented as percentage, mean±SD, or median. Frequency was compared using Pearson's chi-squared test, means were compared using Student’s t-test, and medians using the Kruskal-Wallis test. Hazard ratios (HR) were calculated with a Cox proportional hazard model. CHA2DS2-VASc score components were included as explanatory variables in the multivariate analysis (model 1). In an additional analysis, CHADS2 score components were used instead of CHA2DS2-VASc score components as explanatory variables (model 2). P<0.05 was regarded as statistically significant. All statistical analysis was done using SAS version 9.1 (SAS Institute, Cary, NC, USA).
Novel anticoagulants were approved for use in Japan, only warfarin was used as an anticoagulant. The daily dose of warfarin was larger in the paroxysmal AF group than in the permanent AF group, but the baseline international normalized ratio (INR) of prothrombin time was only slightly lower in the paroxysmal AF group than in the permanent AF group.

**Thromboembolic and Bleeding Events**

There were 126 thromboembolic events during the 2-year follow-up period (Table 3). Among the patients with CHADS2 or CHA2DS2-VASc scores of 0 or 1, the event rate did not differ among the 3 AF groups. Among the patients with CHADS2 or CHA2DS2-VASc scores ≥2, however, the event rate was higher in the permanent AF group than in the paroxysmal AF group (Table 3). Consequently, the crude rate of thromboembolic events was 2-fold higher in the permanent AF group (2.29%/2 years) than in the paroxysmal AF group (1.16%/2 years, P=0.001). The persistent AF group had a similar event rate (1.20%/2 years) to the paroxysmal AF group. On multivariate analysis (model 1), persistent AF emerged as a negative predictor of thromboembolic events, but permanent AF had a

## Results

A total of 110 (1.5%) of 7,516 NVAF patients were lost to follow-up, therefore the remaining 7,406 patients constituted the study group for subsequent analysis.

### Clinical Characteristics

Compared with the permanent AF patients, those with paroxysmal AF were younger and had lower prevalences of male gender, heart failure, diabetes mellitus, and prior history of cerebral infarction or TIA (Table 1). Consequently, the proportion of patients with CHADS2 score of 0 was higher in the paroxysmal AF group than in the permanent AF group, and the mean CHADS2 score was lower in the paroxysmal AF group than in the permanent AF group. This was also true for the CHA2DS2-VASc score.

### Anti-Thrombotic Treatment

Anti-thrombotic treatment was used less frequently in the paroxysmal AF group than in the permanent AF group at baseline (Table 2). Given that the present registry was started before novel anticoagulants were approved for use in Japan, only warfarin was used as an anticoagulant. The daily dose of warfarin was larger in the paroxysmal AF group than in the permanent AF group, but the baseline international normalized ratio (INR) of prothrombin time was only slightly lower in the paroxysmal AF group than in the permanent AF group.

### Thromboembolic and Bleeding Events

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**Table 2. Baseline Anti-Thrombotic Treatment**

<table>
<thead>
<tr>
<th>Type of AF</th>
<th>Paroxysmal (n=2,835)</th>
<th>Persistent (n=1,081)</th>
<th>Permanent (n=3,490)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>326 (11.5)</td>
<td>28 (2.6)</td>
<td>69 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>682 (24.1)</td>
<td>266 (24.6)</td>
<td>989 (28.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2,228 (78.6)</td>
<td>973 (90.0)</td>
<td>3,203 (91.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dose (mg/day)</td>
<td>3.0</td>
<td>2.75</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR &lt;1.6</td>
<td>630 (28.3)</td>
<td>261 (26.8)</td>
<td>779 (24.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>1.6–1.99</td>
<td>787 (35.3)</td>
<td>332 (34.1)</td>
<td>1,229 (38.4)</td>
<td></td>
</tr>
<tr>
<td>2.0–2.59</td>
<td>623 (28.0)</td>
<td>311 (32.0)</td>
<td>920 (28.7)</td>
<td></td>
</tr>
<tr>
<td>2.6–2.99</td>
<td>137 (6.1)</td>
<td>38 (3.9)</td>
<td>188 (5.9)</td>
<td></td>
</tr>
<tr>
<td>≥3.0</td>
<td>51 (2.3)</td>
<td>31 (3.2)</td>
<td>87 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Median INR</td>
<td>1.83</td>
<td>1.83</td>
<td>1.86</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Data given as n (%) or median. AF, atrial fibrillation; INR, international normalized ratio of prothrombin time in patients receiving warfarin.

**Table 3. Thromboembolic and Bleeding Events During 2-Year Follow-up**

<table>
<thead>
<tr>
<th>Type of AF</th>
<th>Paroxysmal (n=2,835)</th>
<th>Persistent (n=1,081)</th>
<th>Permanent (n=3,490)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>33</td>
<td>13</td>
<td>80</td>
<td>0.001</td>
</tr>
<tr>
<td>TIA</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>CHADS2 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (0.7)</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>1</td>
<td>13 (1.2)</td>
<td>4 (1.1)</td>
<td>16 (1.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>≥2</td>
<td>16 (1.4)</td>
<td>9 (1.8)</td>
<td>61 (3.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>1</td>
<td>3 (0.7)</td>
<td>2 (1.2)</td>
<td>1 (0.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>≥2</td>
<td>29 (1.3)</td>
<td>11 (1.3)</td>
<td>78 (2.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>41</td>
<td>20</td>
<td>79</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Data given as n (%). Abbreviations as in Table 1.
similar risk to paroxysmal AF (Table 4). Additionally, age ≥75 years, heart failure and hypertension emerged as independent risks of thromboembolic events (Table 4). Warfarin use was a negative predictor with marginal significance (P=0.0552).

When CHADS2 score was used instead of CHA2DS2-VASc score (model 2), age ≥75 years, heart failure, hypertension, persistent AF, and warfarin emerged as predictors of thromboembolism (Table 4). Again, permanent AF had a similar risk to paroxysmal AF.

There were 140 major hemorrhagic events during the 2-year follow-up period. The permanent AF group had a higher incidence of major hemorrhage with marginal significance (P=0.059; Table 3).

**Discussion**

Thromboembolic events occurred more frequently in the permanent AF group, in particular in patients with higher CHADS2 or CHA2DS2-VASc score. After adjusting for CHA2DS2-VASc score components and warfarin use at baseline, however, the risk of thromboembolic events did not differ between paroxysmal and permanent AF. Our previous subanalysis of the J-RHYTHM Registry found that permanent AF was an independent risk for thromboembolic events, but several important clinical characteristics that affect the risk of such events, for example, coronary artery disease, heart failure, diabetes mellitus, and hypertension, were not included as explanatory variables in that subanalysis because the associated univariate P-values were ≥0.25. This could explain, at least in part, the difference between the results of the present and previous studies.

**Thromboembolic Events in Paroxysmal vs. Permanent AF**

The Stroke Prevention in Atrial Fibrillation study found that the frequency of ischemic stroke was similar among patients with intermittent and sustained AF who were treated with aspirin. In addition, the ACTIVETE W substudy showed that patients with paroxysmal AF treated with anti-thrombotic drugs were at similar risk of thromboembolic events to those with sustained AF. Other studies have also indicated that thromboembolic risk does not differ between paroxysmal and persistent/permanent AF. Consequently, the guidelines for the management of AF in Western countries recommend anticoagulation therapy for patients with paroxysmal AF based on associated clinical risk factors, as is the case for those with permanent AF.

Recently, however, some studies compared the effects of new oral anticoagulants with warfarin in a clinical trial setting and indicated that the event rate of stroke and systemic embolism was lower in patients with paroxysmal AF than in those with persistent or permanent AF. In a substudy of the patients in the SPORTIF III and V trials the HR for stroke/systemic embolism in persistent AF (vs. paroxysmal AF) was 1.87 (95% confidence interval [95% CI]: 1.04–3.36; P=0.037). When the analysis was confined to patients who are at higher risk of stroke/systemic embolism (ie, those with ≥2 stroke risk factors), however, the adjusted HR was only marginally significant (1.68; 95% CI: 0.91–3.1, P=0.098). In a substudy of the ARISTOTLE trial on warfarin vs. apixaban the frequency of stroke or systemic embolism was significantly higher among patients with persistent or permanent AF than among those with paroxysmal AF (1.52% vs. 0.98%, adjusted P=0.015).

Those 2 studies included both ischemic and hemorrhagic strokes as primary endpoints, whereas the present analysis of the J-RHYTHM Registry included only ischemic stroke and systemic embolic events. The present subanalysis clearly shows that after adjusting for CHA2DS2-VASc score components and warfarin use, similar risk of thromboembolic events was seen in the paroxysmal and permanent groups. This was also true when CHADS2 score was used instead of CHA2DS2-VASc score. At first glance, it seems difficult to explain the different results obtained by the present and previous studies.

The previous clinical trials, however, were randomized studies, included both hemorrhagic and ischemic strokes as endpoints, and enrolled patients who were receiving anticoagulants. In the ARISTOTLE trial, the mean CHADS2 scores of the paroxysmal AF and persistent/permanent AF patients were 2.0 and 2.1, respectively, whereas in the present study the mean CHADS2 scores of the paroxysmal, persistent, and permanent AF patients were 1.42, 1.60, and 1.90, respectively; thus, differences in the underlying risk level of thromboembolic events might also have contributed to the differences between the findings of the present and previous studies.

The present finding that the persistent AF group had a lower HR than the paroxysmal AF group (Table 4) is difficult to
explain. The duration and frequency of episodes of AF would also have affected the results, but this information was not included in the J-RHYTHM Registry.\textsuperscript{13,14}

**Hemorrhagic Events and Type of AF**

Rates of major hemorrhagic events were not markedly different with type of AF in previous studies. The ACTIVE-W sub-study noted that patients with paroxysmal AF treated with oral antiocoagulation had a slightly higher rate of major hemorrhagic events as compared to those with sustained AF (3.2 vs. 2.0/100 person-years).\textsuperscript{3} Other studies reported that the risk of major hemorrhagic events was similar between paroxysmal and persistent/permanent AF.\textsuperscript{4,5,7} In the present study there was a trend toward a higher rate of major hemorrhagic events in the permanent AF group as compared to the paroxysmal AF group with marginal significance (Table 3). Taken together, type of AF would not critically affect major hemorrhagic events among patients treated with oral anticoagulation.

**Study Limitations**

The present study had several limitations. First, the selection of explanatory variables affected the results of the multivariate analysis. Our previous subanalysis of the J-RHYTHM Registry found that permanent AF was an independent risk factor for thromboembolic events,\textsuperscript{6} but the present subanalysis produced a different result. Therefore, the results of post-hoc analyses should be interpreted cautiously, even when multivariate analysis is used. Second, the choice of anti-thrombotic drugs and doses was left to the discretion of the treating physicians; hence, the effects of changes in anti-thrombotic treatment were not included in analysis, and the quality of anticoagulation control with warfarin, for example, the time in the therapeutic range,\textsuperscript{21} was not taken into consideration. Only warfarin was used for anticoagulation in the present study; therefore the result would be modified if novel oral anticoagulants\textsuperscript{27} were used. Third, although patients who had been in sinus rhythm for 1 year were not included in the present registry, the frequency and duration of AF episodes, which might have affected the embolic event rate,\textsuperscript{23–25} were not determined in the paroxysmal or persistent AF groups. Finally, a change in the type of AF (eg, from paroxysmal to permanent AF) could also have affected the event rates, but this was not assessed in the present analysis.

**Conclusions**

Although the present study had the aforementioned limitations, it has shown that crude rate of thromboembolic events was higher in permanent NVAF than in paroxysmal NVAF among Japanese patients who were mostly treated with warfarin. After adjusting for CHA2DS2-VASc components and warfarin use, however, the risk of thromboembolic events did not differ between paroxysmal and permanent NVAF. This was also true when CHADS2 score was used for the adjustment instead of CHA2DS2-VASc score. Anticoagulation should be given to patients with paroxysmal NVAF, as it is to those with permanent NVAF, based on thromboembolic risk level.

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**Disclosures**

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**References**


**Appendix**

The participating physicians are listed in references 13 and 14.