Incidence of Major Bleeding Complication of Warfarin Therapy in Japanese Patients With Atrial Fibrillation

Shinya Suzuki, MD; Takeshi Yamashita, MD; Takeshi Kato, MD; Tadashi Fujino, MD; Koichi Sagara, MD; Hitoshi Sawada, MD; Tadanori Aizawa, MD; Long-Tai Fu, MD

Background During anticoagulation for prevention of stroke in patients with non-valvular atrial fibrillation (NVAF), bleeding is the most serious complication. In Western countries, the incidences of major bleeding and intracranial hemorrhages with low-dose warfarin are known to occur at a rate of 0.4–1.3% and 0.2% per year, respectively. The purpose of this study was to investigate the incidence and risk factors for major bleeding related with warfarin therapy in Japanese patients with NVAF.

Methods and Results From August 2004 to July 2005, 667 NVAF patients treated with warfarin for NVAF were followed-up. The target prothrombin time-international normalized ratio (PT-INR) value was set at 1.6–2.6 (low-dose warfarin). The exposure on warfarin was 503 patient-years (average PT-INR 2.0±0.40). During the follow-up period, 12 major bleeding complications occurred (2.38% per patient-year), which included 3 intracranial hemorrhages (0.60% per patient-year). Among the patients' characteristics, average PT-INR ≥2.27 during the study was identified as an independent risk factor for major bleeding.

Conclusions The incidence of major bleeding and intracranial hemorrhages in Japanese NVAF patients with low-dose warfarin therapy was 2.38% and 0.60% per patient-year, respectively, which is higher than in Westerners. (Circ J 2007; 71: 761–765)

Key Words: Anticoagulants; Atrial fibrillation; Japanese patients; Warfarin

Methods

Study Patients

From the database of outpatients who visited the Cardiovascular Institute Hospital between August 2004 and July 2005, we screened all patients with NVAF under warfarin treatment and identified 667 patients (444 males, 223 females, 68.4±10.6 years old, 566 paroxysmal AF). In the present study, NVAF was defined as AF without rheumatic valvular diseases, and the target PT-INR value was set at 1.6–2.6 for the prevention of stroke associated with NVAF irrespective of the patient's backgrounds.

Data Collection

We collected the following information from the computerized database: gender, age, use of aspirin, PT-INR value at each hospital visit, type of AF (paroxysmal or persistent) and coexisting conditions including hypertension and diabetes mellitus. The average PT-INR value during the study period was determined as the mean of all the PT-INR values measured in each patient.

Adverse Events of Anticoagulation

Although major bleeding usually includes fatal bleeding, bleeding that required blood transfusion, and intracranial hemorrhages in the previous studies bleeding that requires emergent hospitalization has been the most common category used as an equivalent term for major bleeding. On the other hand, intracranial hemorrhages have always been counted as one of the most significant hemorrhagic events. In the present study, to compare the incidence of hemorrhagic events with previous studies, major bleeding was defined as bleeding that required emer-

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The Cardiovascular Institute, Tokyo, Japan
Mailing address: Shinya Suzuki, MD, The Cardiovascular Institute, 7-3-10 Roppongi, Minato-ku, Tokyo 106-0032, Japan. E-mail: sinsuz@umin.ac.jp

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gent hospitalization, and intracranial hemorrhages were also counted as the other category.

Data Analysis
The incidences of major bleeding and intracranial hemorrhages were calculated as values per patient-year in the total patient cohort. The incidence of adverse events and the 95% confidence intervals (CIs) were derived assuming a Poisson distribution of the number of events. Thereafter, each result was correlated with patients’ backgrounds, including gender, age, average PT-INR value, use of aspirin, type of AF (paroxysmal or persistent) and coexisting conditions, using chi-square test and logistic regression analysis. Data are presented as mean ± SD. Statistical significance was set at p<0.05.

Ethical Issues
The Ethical Committee of the Cardiovascular Institute granted permission for this study.

Results
Adverse Events of Anticoagulation (Tables 1,2)
In the present study, 667 patients received warfarin therapy for stroke prevention (503 patient-years). The average PT-INR value was 2.00±0.40, almost identical to the target PT-INR value for the study. During the investigated 1-year period, 12 major bleeding events occurred: 3 intracranial hemorrhages (1 intracerebral, 1 subarachnoid, 1 subdural hemorrhage) and 9 extracranial hemorrhages (6 gastrointestinal hemorrhages, 2 hematuria, 1 hemoptysis). Three of the 6 cases of gastrointestinal hemorrhages and the single case of hemoptysis required blood transfusion. One of the 3 intracranial hemorrhages was fatal. As a result, the incidence of major bleeding was 2.38% per patient-year (95% CI 1.36–4.17), and that of intracranial hemorrhages was 0.60% per patient-year (95% CI 0.20–1.75).

Effects of Gender and Age
When we divided the patients by gender, the incidence of adverse events tended to be greater in males than in females (Fig 1A), although there was no significant statistical difference.

Effects of Average PT-INR Value and Aspirin Cotherapy
The PT-INR value is also known to affect the occurrence of major bleeding.8 When we compared patients in the 25% upper quartile of the average PT-INR value (average PT-INR ≥2.27) with those in the other quartiles (average PT-INR <2.27), the incidence of major bleeding tended to be more frequent in patients ≥75 years old than those <75 years old (Fig1B), although the difference did not reach statistical significance.

Effects of Type of AF and Coexisting Conditions
Although it is known that coexisting conditions, such as hypertension and diabetes mellitus, are risk factors for stroke8 and that the stroke incidence is similar in paroxysmal and persistent AF11 the effects of these clinical variables on bleeding events are unknown.

When we compared the incidence of hemorrhages between patients with and without hypertension and diabetes mellitus, it was not related to the presence of these varia-

Table 1 Patients’ Characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intensity of anticoagulation</th>
<th>Male, %</th>
<th>Age, Mean±SD, years</th>
<th>No. of subjects</th>
<th>No. of patient-years</th>
<th>No. of major bleeding events</th>
<th>Intracranial bleeding, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.6–2.6</td>
<td>67</td>
<td>68±11</td>
<td>667</td>
<td>503.0</td>
<td>12 (2.4)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>LDW</td>
<td>1.6–2.6</td>
<td>64</td>
<td>68±11</td>
<td>457</td>
<td>354.0</td>
<td>9 (2.5)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>LDWA</td>
<td>1.6–2.6</td>
<td>71</td>
<td>69±11</td>
<td>210</td>
<td>149.0</td>
<td>3 (2.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

LDW, adjusted low-dose warfarin; LDWA, adjusted low-dose warfarin and aspirin.

Table 2 Adverse Events During Warfarin Therapy

<table>
<thead>
<tr>
<th>Age/ gender</th>
<th>Average PT-INR</th>
<th>Aspirin cotherapy</th>
<th>Event</th>
<th>Transfusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>76/M</td>
<td>2.59</td>
<td>(–)</td>
<td>Intracranial hemorrhage</td>
<td>(–)</td>
<td>Subarachnoid hemorrhage, fatal</td>
</tr>
<tr>
<td>65/M</td>
<td>2.45</td>
<td>(–)</td>
<td>Intracranial hemorrhage</td>
<td>(–)</td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>44/M</td>
<td>1.90</td>
<td>(–)</td>
<td>Intracranial hemorrhage</td>
<td>(–)</td>
<td>Subdural hemorrhage</td>
</tr>
<tr>
<td>83/F</td>
<td>1.86</td>
<td>(–)</td>
<td>GIT hemorrhage</td>
<td>(+)</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>81/F</td>
<td>2.25</td>
<td>(+)</td>
<td>GIT hemorrhage</td>
<td>(–)</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>73/M</td>
<td>2.24</td>
<td>(–)</td>
<td>GIT hemorrhage</td>
<td>(–)</td>
<td></td>
</tr>
<tr>
<td>69/M</td>
<td>2.38</td>
<td>(+)</td>
<td>GIT hemorrhage</td>
<td>(+)</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>66/M</td>
<td>1.89</td>
<td>(+)</td>
<td>GIT hemorrhage</td>
<td>(+)</td>
<td>Mallory-Weiss syndrome</td>
</tr>
<tr>
<td>66/M</td>
<td>2.34</td>
<td>(–)</td>
<td>GIT hemorrhage</td>
<td>(–)</td>
<td>Gastritis</td>
</tr>
<tr>
<td>79/M</td>
<td>2.48</td>
<td>(+)</td>
<td>Hematuria</td>
<td>(–)</td>
<td></td>
</tr>
<tr>
<td>70/M</td>
<td>2.66</td>
<td>(–)</td>
<td>Hematuria</td>
<td>(–)</td>
<td>Prostatic cancer</td>
</tr>
<tr>
<td>81/M</td>
<td>2.46</td>
<td>(–)</td>
<td>Hemoptysis</td>
<td>(+)</td>
<td>Pneumoniae</td>
</tr>
</tbody>
</table>

PT-INR, prothrombin time-international normalized ratio; GIT, gastrointestinal tract.
blees (Figs 1E,F). Also, the type of AF did not affect the incidence of bleeding events, which tended to be higher in those with persistent AF (Fig 1G).

**Adjusted Odds Ratio**

To evaluate the independent effects of these variables on the incidence of hemorrhages, we determined the adjusted odds ratios using multiple logistic regression analysis (Table 3) with the addition of the duration of warfarin treatment as an adjusting factor. Among the 8 factors, average PT-INR value $\geq 2.27$ was the only independent risk factor associated with the occurrence of major bleeding. The
Events became increasingly frequent when the PT-INR was <1.6, whereas hemorrhagic strokes. In fact, a meta-analysis of 5 major studies for the prevention of stroke, but also increases the risk of hemorrhages. In particular, the incidence of major bleeding was 2.38% per patient-year, and (2) the average PT-INR value ≥2.27 was an independent risk factor for major bleeding in this particular population.

Incidence of Hemorrhage With Anticoagulation
Recent studies from Western countries have reported that the incidence of major bleeding under warfarin therapy for NVAF is 1.6–2.5% per year with standard-dose warfarin;6–9 however, a lower incidence of 0.4–1.3% per year has been reported with adjusted low-dose warfarin.3,4 In the present study, with adjusted low-dose warfarin in Japanese patients, the incidence was 2.38% per year, which was higher in Western countries. These results suggest that there are racial differences in the bleeding tendency under warfarin.

Average PT-INR Value
High-intensity control of anticoagulation leads to reduction of the risk of stroke, but also increases the risk of hemorrhages. In fact, a meta-analysis of 5 major studies for the primary prevention of stroke in NVAF patients in Western countries12 has reported that thromboembolic events increased when the PT-INR was <2.0, whereas hemorrhagic events became increasingly frequent when it was ≥3.0.

In contrast, a previous study from Japan for secondary prevention of stroke13 reported that thromboembolic events increased when the PT-INR was <1.6, whereas hemorrhagic events became increasingly frequent when it was ≥2.6. Interestingly, the study demonstrated that major bleeding occurred particularly in patients under warfarin therapy with a PT-INR ≥2.3.

In the present study of patients undergoing primary prevention of stroke, PT-INR ≥2.27 was the upper quartile and the subset was the independent risk factor for the incidence of major bleeding. Though it is an artificial figure derived from the quartile of patients, the value was almost identical with that in the previous study. The figure of ≥2.27–2.3 might be particularly meaningful for Japanese NVAF patients.

### Discussion

**Major Findings**
The major findings of the present study are as follows: (1) the total incidence of major bleeding was 2.38% per patient-year in Japanese AF patients under a target PT-INR of 1.6–2.6, and that of intracranial hemorrhages was 0.86% per patient-year, and (2) the average PT-INR value ≥2.27 was an independent risk factor for major bleeding in this particular population.

**Other Factors**
According to previous studies, age8,14 and use of aspirin15–21 are independent predictors of major bleeding associated with warfarin treatment for NVAF. Hypertension and diabetes mellitus are also known to be independent predictors of stroke associated with NVAF. Moreover, paroxysmal AF and persistent AF are thought to be equivalent risk factors for stroke.13 When we evaluated the role of these factors, we could not demonstrate significant relationships between these factors and the incidence of major bleeding. However, that may be related to the relatively small number of patients.

**Study Limitations**
First, the number of patients was rather small and the observation period was relatively short. Second, the incidence of stroke could not be evaluated. The intensity of control by warfarin should be discussed according to the balance between risks and benefits. Third, because the present study was retrospective, the incidence of adverse events should be carefully compared with other large scale clinical trials, which might involve lower-risk patients for adverse events than those in observational studies such as the present one.

Although limited for these reasons, the present study has identified the incidence of hemorrhagic events under anticoagulation in Japanese patients and suggests some racial difference in the bleeding tendency under warfarin. More investigations are necessary to develop the appropriate control level of anticoagulation therapy for prevention of stroke in Japanese AF patients.

### References


