Optimal Intensity of International Normalized Ratio in Warfarin Therapy for Secondary Prevention of Stroke in Patients with Non-valvular Atrial Fibrillation

Masahiro Yasaka, Kazuo Minematsu and Takenori Yamaguchi

Abstract

Objective To determine optimal intensity of international normalized ratio (INR) of warfarin therapy for the prevention of ischemic events in patients with non-valvular atrial fibrillation (NVAF), we evaluated the risk of severe recurrent stroke, systemic embolism and major hemorrhagic complications according to INR and age.

Methods We carried out the National Cardiovascular Center (NCVC) NVAF Secondary Prevention Study and analyzed data with those of Japanese Nonvalvular Atrial Fibrillation-embolism Secondary Prevention Cooperative Study to elucidate relationships of major stroke and hemorrhage with INR and age. In both studies, all patients with cardioembolic stroke were given warfarin, monitored with INR every month, and followed up for primary endpoints of stroke and embolism to other parts of the body, and for secondary endpoints of major hemorrhagic complications requiring blood transfusion or hospitalization. We regarded ischemic stroke with NIH stroke scale (NIHSS) score ≥10 or systemic embolism as a major ischemic event and ischemic stroke with NIHSS score <10 as a minor ischemic event. There were 203 patients enrolled in total (152 men and 51 women). We investigated the relationship of occurrence of the events with INR and age, and calculated the incidence rates of major and minor ischemic events and major hemorrhagic events.

Results During the mean follow-up of 653 days, major ischemic stroke and systemic embolism occurred in only 4 patients with INR <1.6, minor ischemic stroke in 10 patients with INR 1.50–2.66, and major hemorrhage in 9 patients with INR 2.30–3.56. Patients with major ischemic or hemorrhagic events were significantly older than those without any events (75±4 years vs. 67±7 years, p<0.001 unpaired t test). Incidence rates of any events at INR ≤1.59, 1.60–1.99, 2.00–2.59 and ≥2.60 were 8.6%, 3.8%, 4.9%, and 25.7%/year, respectively.

Conclusions Major ischemic or hemorrhagic events occur often in the elderly NVAF patients, in whom an INR value of between 1.6 and 2.6 seems optimal to prevent such events.

Key words: cardioembolic stroke, systemic embolism, hemorrhagic complication, elderly, Japanese

Introduction

The efficacy of anticoagulation for primary prevention of stroke or transient ischemic attacks (TIA) in patients with nonvalvular atrial fibrillation (NVAF) has been established by five prospective, randomized and controlled trials (1–5). Thus, warfarin treatment using international normalized ratios (INR) ranging from 2.0 to 3.0 (or 4.0) is recommended for NVAF patients, who have any of the following risk factors; history of previous stroke or TIA, diabetes mellitus, hypertension, advanced age (≥75 years old), congestive heart failure, and coronary artery disease (6–8).

The efficacy of warfarin treatment for secondary prevention of stroke in NVAF patients has been evaluated by three prospective studies, European Atrial Fibrillation Trial (EAF), Stroke Prevention in Atrial Fibrillation III randomized clinical trial (SPAF III) and Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study (9–11). The EAF study reported that warfarin treatment with INR ranging from 2.5 to 4.0 was effective for secondary prevention, because of the risk reduction of ischemic stroke from 12% to 4% per year and a low incidence of major hemorrhagic events (2.8%/year) (9). All hemorrhagic complications, however, were observed more frequently in the anticoagulation group than in the control group (hazard ratio 3.4, 95% CI 1.9–6.0, p<0.001). Although the risk of stroke is high in NVAF patients with a history of stroke, the INR range used in the European study seems inappropriately high when compared both to the recom
mended INR range for primary prevention and to the ordinary
INR level applied to elderly patients. The study indicated that
no treatment effect was apparent with anticoagulation below
an INR of 2.0 (12). However, the conclusion was obtained by
comparing the event rate in a group of patients with INR be-
tween 1.0 and 1.9 with those in other groups of patients with
INR above 2.0. The efficacy was not assessed by further divid-
ing the group of INR between 1.0 and 1.9.

A major hemorrhage often develops in elderly patients on
anticoagulation therapy while the lowest intensity to effectively
prevent ischemic stroke has not been clearly determined. Ac-
cordingly, anticoagulation with warfarin is controversial for
the treatment of elderly patients with NVAF. Recently, a
multicenter, prospective, randomized study from Japan dem-
strated that the low intensity warfarin treatment (INR 1.5 to
2.1) for prevention of stroke recurrence was safer than the con-
ventional intensity treatment (INR 2.2 to 3.5) in the elderly
(11). However, because recurrent stroke was seen in only one
out of 46 patients aged 70 or more in the study, the lowest
intensity of warfarin treatment in the elderly to prevent ischemic
stroke is still unknown.

Stroke prevention in atrial fibrillation III (SPAF III) study
demonstrated that very low intensity warfarin treatment (INR
1.2–1.5) was not useful to prevent recurrent stroke in NVAF
compared to conventional warfarin therapy (INR 2.0–3.0) (10,
13). This study indicated partial efficacy of warfarin control
with INR between 1.6 and 1.9.

We found by a retrospective study that anticoagulant therapy
with INR ≥1.6 effectively prevented a large infarct and poor
outcome, even when ischemic stroke did occur in patients with
an embolicigenic heart disease (14).

To determine optimal intensity of INR for secondary pre-
vention of major ischemic and hemorrhagic events, we pro-
spectively conducted National Cardiovascular Center (NCVC)
NVAF Secondary Prevention Study and analyzed data with
those of Japanese Nonvalvular Atrial Fibrillation-embolism
Secondary Prevention Cooperative Study (11).

For editorial comment, see p 1166.

Methods

We recruited NVAF patients at the outpatient clinic of the
Cerebrovascular Division of NCVC in July and August of 1998,
who had a history of ischemic stroke or TIA more than one
month prior to the enrollment, and were undergoing antico-
agulant therapy for secondary prevention (NCVC NVAF Sec-
ondary Prevention Study).

We excluded patients, who had intracardiac thrombus, left
ventricular aneurysm, severe congestive heart failure
(NYHA=4), infective endocarditis, acute myocardial infarc-
tion (≤30 days), recent coronary artery bypass grafting (≤30
days), recent percutaneous transluminal coronary angioplasty
(≤30 days), dilated cardiomyopathy, mitral valve prolapse,
sick sinus syndrome, hyperthyroidism, severe renal or liver
diseases, any other thrombotic disorders, pregnancy, or can-
cer.

After a written informed consent was obtained from patients
or their family, patients were enrolled in the study. We obtained
patients’ clinical history in terms of hypertension, diabetes
mellitus, continuous or paroxysmal atrial fibrillation, angina
pectoris, myocardial infarction, and number of past episodes
of stroke.

Hypertension was defined as the use of antihypertensive
agents or blood pressure recordings with systolic ≥160 mmHg
or diastolic ≥95 mmHg. Diabetes mellitus was defined as use
of insulin or oral hypoglycemic agents, fasting blood glucose
levels ≥140 mg/dl, or random blood glucose levels ≥200 mg/dl.

The enrolled patients were evaluated for two years for isch-
emic and major hemorrhagic events by expert stroke physi-
ocians once a month with monitoring INR. Ischemic events in-
cluded brain infarction, TIA, and embolism to other parts of
the body. We regarded ischemic stroke with NIH stroke scale
(NIHSS) score ≥10 or systemic embolism as major ischemic
events and ischemic stroke with NIHSS score <10 as minor
ischemic events. Mean values of INR before and just after the
events were counted as an INR associated with the events. We
regarded the mean INR value of two continuous sampling points
as a representative INR during the period between the two sam-
ppling points. Then, we calculated the incidence rate (per 100
person years) of ischemic and hemorrhagic events by INR
≤1.59, 1.60–1.99, 2.00–2.59 and ≥2.60.

Major hemorrhagic complications were brain hemorrhage,
retinal hemorrhage, or other severe hemorrhagic complications
that were fatal or required hospital admission for emergency
treatment or blood transfusion. Patients were followed for 24
months, or until any ischemic or major hemorrhagic events
occurred. The target intensity of INR was decided by the phy-
ician in charge. Modified-Rankin scale score was obtained at
entry and 3 months after the endpoint event (15). At the time of
admission due to endpoint of brain infarction or brain hemor-
hage, the NIHSS score was evaluated (16).

The Japanese NVAF-Embolism Secondary Prevention Co-
oporative Study was conducted between April 1994 and March
1998 in 19 institutions in Japan (11). They recruited 115 pa-
tients aged 66.7±6.5 year and randomly allocated 55 patients
to a conventional intensity group (target INR 2.2 to 3.5) and 60
to low intensity group (target INR 1.5 to 2.1). The trial was
stopped after a follow-up of 658±423 days, when major hem-
orrhagic complication occurred in 6 patients of the conven-
tional intensity group and the frequency (6.6%/year) was sig-
nificantly higher than that in the low intensity group (0%/year,
p=0.01, Fisher’s exact test). Because they did not evaluate score
of NIHSS at onset of stroke, we regarded stroke with socially
independent or independent at home as minor stroke and de-
pendent at home or worse as major stroke. We re-calculated a
mean INR associated with any events and intensity of INR by
person-years according to the same method used in the NCVC
NVAF Secondary Prevention Study.

Continuous data were expressed as mean±SD. We used un-
paired t test and chi square test for analysis of continuous and discrete variables, respectively. In cases with low cell counts of less than five, Fisher’s exact test was used instead of the chi square test.

Results

A total of 88 NVAF patients (69 men and 19 women, 69.3±7.7 years old) were enrolled in the NCVC NVAF Secondary Prevention Study. Demographics of the patients at entry are shown in Table 1.

During the study period of two years, there were 14 patients who developed ischemic or major hemorrhagic events and three patients dropped out. The mean follow-up period was 646±219 days (Table 2). The ischemic events were seen in 11 patients, four were major ischemic events and the other seven were minor ischemic events (Table 3). Their INR associated with the major ischemic events were all less than 1.6 (1.27, 1.34, 1.53, and 1.55), although INR associated with minor ischemic events ranged between 1.50 and 2.66 (1.50, 1.61, 1.65, 1.73, 1.80, 2.41, and 2.66). Out of the four patients with major ischemic events, three had major strokes (NIHSS at admission ≥10) and one suffered a fatal embolism to the mesenteric artery. Their modified Rankin scale scores at entry deteriorated at 3 months after the endpoints from 0 to 4, 0 to 3, 1 to 4, and 2 to dead, respectively. In the seven patients with minor ischemic events, the modified Rankin scale scores at entry were 0 in three of them and 1 in three and 2 in the other one. Their scores did not change 3 months after the endpoints in six patients, but the score increased from 1 to 2 in the remaining one.

There were three patients who developed major hemorrhagic complications, brain hemorrhage in two and subdural hematoma with INR of 2.44, 2.94 and 3.18, respectively. Their modified Rankin scale scores at entry were 1, 1, and 2 and those at 3 months after the endpoint were 4, 1, and 4, respectively. Minor bleeding was seen in sixteen patients.

When we combined the two studies, the current study (NCVC NVAF Secondary Prevention Study) and the previous

<table>
<thead>
<tr>
<th>Table 1. Demographics at Entry</th>
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<tbody>
<tr>
<td><strong>NCVC NVAF Secondary Prevention Study</strong></td>
<td><strong>Japanese NVAF-Embolism Secondary Prevention Cooperative Study (11)</strong></td>
</tr>
<tr>
<td><strong>n=88</strong></td>
<td><strong>n=115</strong></td>
</tr>
<tr>
<td>Age (year)</td>
<td>69.3±7.7</td>
</tr>
<tr>
<td>Men/Women</td>
<td>69/19</td>
</tr>
<tr>
<td>Fixed/Paroxysmal AF</td>
<td>59/29</td>
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<tr>
<td>Hypertension</td>
<td>48 (54.5%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (18.2%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6 (6.8%)</td>
</tr>
<tr>
<td>Multiple episodes of stroke</td>
<td>25 (28.1%)</td>
</tr>
<tr>
<td>Modified Rankin Scale at entry, median (range)</td>
<td>0 (0-4)</td>
</tr>
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</table>

NCVC: National Cardiovascular Center, NVAF: non-valvular atrial fibrillation, AF: atrial fibrillation.

<table>
<thead>
<tr>
<th>Table 2. Demographics of Results</th>
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<td><strong>NCVC NVAF Secondary Prevention Study</strong></td>
<td><strong>Japanese NVAF-Embolism Secondary Prevention Cooperative Study (11)</strong></td>
</tr>
<tr>
<td><strong>n=88</strong></td>
<td><strong>n=115</strong></td>
</tr>
<tr>
<td>PT (INR)</td>
<td>1.99±0.24</td>
</tr>
<tr>
<td>Follow-up period (days)</td>
<td>646±219</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130.8±9.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.1±5.5</td>
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<tr>
<td>Events</td>
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</tr>
<tr>
<td>Ischemic events</td>
<td>11</td>
</tr>
<tr>
<td>Major ischemic events</td>
<td>4</td>
</tr>
<tr>
<td>Minor ischemic events</td>
<td>7</td>
</tr>
<tr>
<td>Major hemorrhagic events</td>
<td>3</td>
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NCVC: National Cardiovascular Center, NVAF: non-valvular atrial fibrillation, INR: international normalized ratio.
### Table 3. Ischemic Events

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (mo)</th>
<th>Sex</th>
<th>Endpoint</th>
<th>Territory, lesion</th>
<th>Interval from entry (mo)</th>
<th>INR</th>
<th>NIHSS on admission at entry</th>
<th>Modified Rankin scale 3 months after endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>F</td>
<td>Brain infarction</td>
<td>Lt MCA, cortex</td>
<td>8</td>
<td>1.34</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>F</td>
<td>Brain infarction</td>
<td>Lt MCA, cortex</td>
<td>7</td>
<td>1.27</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>F</td>
<td>Fatal embolism</td>
<td>mesenteric artery</td>
<td>6</td>
<td>1.53*</td>
<td>-</td>
<td>dead</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>M</td>
<td>Brain infarction</td>
<td>Lt MCA, cortex</td>
<td>8</td>
<td>1.55</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

**Minor ischemic events**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (mo)</th>
<th>Sex</th>
<th>Endpoint</th>
<th>Territory, lesion</th>
<th>Interval from entry (mo)</th>
<th>INR</th>
<th>NIHSS on admission at entry</th>
<th>Modified Rankin scale 3 months after endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>56</td>
<td>M</td>
<td>Brain infarction</td>
<td>Lt MCA, DWM</td>
<td>2</td>
<td>2.41</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>M</td>
<td>TIA</td>
<td>Lt ICA</td>
<td>23</td>
<td>1.73</td>
<td>0</td>
<td>0</td>
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<tr>
<td>7</td>
<td>58</td>
<td>M</td>
<td>Brain infarction</td>
<td>Lt anterior choroidal artery</td>
<td>11</td>
<td>2.54*</td>
<td>-</td>
<td>socially independent at home</td>
</tr>
<tr>
<td>8</td>
<td>58</td>
<td>M</td>
<td>Brain infarction</td>
<td>Lt MCA, cortex</td>
<td>10 days</td>
<td>2.34</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>M</td>
<td>Brain infarction</td>
<td>Mid brain</td>
<td>22</td>
<td>2.66</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>M</td>
<td>Brain infarction</td>
<td>Lt MCA, cortex</td>
<td>18</td>
<td>1.61</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>M</td>
<td>Brain infarction</td>
<td>Pons</td>
<td>9</td>
<td>1.68</td>
<td>-</td>
<td>socially independent</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>M</td>
<td>TIA</td>
<td>Lt ICA</td>
<td>5</td>
<td>1.80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>74</td>
<td>M</td>
<td>Brain infarction</td>
<td>Rt MCA, cortex</td>
<td>2</td>
<td>1.65</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>76</td>
<td>F</td>
<td>Brain infarction</td>
<td>Lt MCA DWM</td>
<td>5</td>
<td>1.50</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

No. 7, 8, and 11 from the previous study (11), *n*: INR before events, Lt: Left, Rt: Right, MCA: middle cerebral artery, ICA: internal carotid artery, DWM: deep white matter, INR: international normalized ratio, NIHSS, NIH stroke scale.

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**Figure 1.** Intensity of anticoagulation and person-years of exposure to various levels of anticoagulant therapy.

**Figure 2.** Intensity of anticoagulation and incidence rates of ischemic and hemorrhagic events. Diamond shaded bar: major ischemic events, upward diagonal shaded bars: minor ischemic events, Black bars: major hemorrhagic events.
Optimal Intensity of INR in NVAF

Table 4. Major Hemorrhagic Events

| Case | Age/sex | Site of lesion (treatment) | Interval from entry (mo) | INR  
|------|---------|----------------------------|--------------------------|-------
| 1    | 67/M    | Gastrointestinal bleeding (blood transfusion) | 4                        | 3.56 
| 2    | 73/M    | Gastrointestinal bleeding, cholecystic cancer (surgical resection of the cancer) | 11                       | 2.59* 
| 3    | 74/M    | Gastrointestinal bleeding (blood transfusion) | 15                       | 2.66* 
| 4    | 74/F    | Massive subcutaneous hemorrhage with accidental fall (surgical resection) | 2                        | 2.80* 
| 5    | 77/M    | Cerebellar hemorrhage (hospitalized medical care) | 33                       | 2.30 
| 6    | 77/M    | Hemothysis (hospitalized medical care) | 3                        | 2.78 
| 7    | 77/F    | Cerebellar hemorrhage (hospitalized medical care) | 4                        | 2.44 
| 8    | 81/M    | Subdural hematoma | 1                        | 3.18 
| 9    | 83/M    | Brain hemorrhage, Lt frontal (hospitalized medical care) | 19                       | 2.94 

No. 1–6 from previous study. INR: international normalized ratio. n*: INR before events.

Discussion

Hylek et al investigated the lowest intensity of anticoagulation that was effective in preventing stroke in NVAF patients in a case control study (17), and found that anticoagulant prophylaxis was effective at INR of 2.0 or greater. However, the risk of stroke rose relatively as the INR decreased below 2.0; the adjusted odds ratio for stroke was 2.0, 3.3 and 6.0 at INRs of 1.7, 1.5, and 1.3, respectively, as compared with the risk at an INR of 2.0. Thus, INR value of 1.7 may provide partial efficacy in preventing stroke in NVAF patients when compared to those of 1.5 or 1.3.

The SPAF III study demonstrated that the annual event rate of ischemic stroke or systemic embolism in a group of patients with INR between 1.5 and 1.9 was lower than those in groups of patients with INR below 1.5 (10). Two randomized prospective studies on the primary prevention of stroke in NVAF patients using 1.4 and 1.5 as the lower limits of target INR, demonstrated the usefulness of anticoagulant therapy with warfarin (2, 5). Although the option of a lower intensity anticoagulation in the elderly than recommended in the younger has been suggested (18), the effect of lower intensity anticoagulation on severity of ischemic events has not been elucidated yet. According to the present study, the lower limit of the intensity of anticoagulation for secondary prevention of severe ischemic events appeared to be approximately 1.6 (Fig. 2). This result was in good agreement with the INR value that had been obtained by the retrospective study comparing INR and the size of brain infarct (14). Anticoagulation with INR between 1.6 and 1.9 may have not only partial efficacy in reducing stroke occurrence (13), but it may also have an effect to prevent major ischemic events.

Minor stroke occurred in not only patients with INR <1.6 but also in those with INR ≥1.6. The failure to prevent minor stroke in patients with INR above 1.6 may be related to the mechanism of stroke recurrence. Although it is well known that cardioembolic stroke is prone to recur (19, 20), some minor strokes from the other causes, such as atherothrombotic or lacunar infarction, may occur even in patients with higher INR. Such strokes are usually less severe and do not respond as well to anticoagulant prevention as cardioembolic stroke.

It has already been reported that the size of intracardiac thrombus was reduced by anticoagulation, which was attributed to the relative predominance of plasma fibrinolytic activity over thrombin activity by anticoagulation (21). Therefore, even when a thrombus is formed in patients with INR ≥1.6, it will probably be small, and even when they develop ischemic stroke, it may result in small brain infarct.

The results of analyzing combined data demonstrated a sharp rise in the incidence of severe hemorrhage in INR ≥2.6 and most patients suffering severe hemorrhage were elderly. Therefore it is recommended to avoid INR ≥2.6 in treating the elderly. This value was consistent with previous suggestions (18).

Although patients were randomly assigned into two groups receiving low or conventional intensity of INR in the Japanese NVAF-Embolism Secondary Prevention Cooperative Study, the level of INR in each patient was determined by the physician in charge in the NCVC-NVAF Secondary Prevention Study. Therefore, the decision of INR level in the latter study may have been affected by bias. It seems that a prospective randomized study is required in a large number of elderly NVAF patients in order to elucidate whether the INR range between 1.6 and 2.6 is more useful than the conventional range of INR between 2.0 and 3.0 in the prevention of stroke in the elderly NVAF patients.

According to the results of two studies, the elderly seem prone to develop major ischemic and hemorrhagic events in INR ≤1.59 and ≥2.60, respectively. The optimal intensity of INR in warfarin therapy for secondary prevention of stroke in elderly patients with NVAF may be between 1.6 and 2.6. This INR range of 1.6 and 2.6 may be quite important in the prevention of major stroke in NVAF elderly people who have a risk of hemorrhage.
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