Intensity of Anticoagulation and Clinical Outcomes in Acute Cardioembolic Stroke

The Fukuoka Stroke Registry

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Background and Purpose—The relationship between the intensity of anticoagulation at the onset of acute cardioembolic stroke and clinical outcome after stroke is unclear. Here, we elucidated the relationship between prothrombin time–international normalized ratio (PT-INR) values on admission and clinical outcomes in patients with acute cardioembolic stroke.

Methods—A total of 602 patients from the Fukuoka Stroke Registry in Japan who had been treated with warfarin but developed cardioembolic stroke were enrolled. The patients were classified into 3 groups according to their PT-INR values on admission: PT-INR <1.50, 411 patients; PT-INR 1.50 to 1.99, 146 patients; and PT-INR ≥2.00, 45 patients. The associations between PT-INR categories and severe neurological deficits (National Institutes of Health Stroke Scale ≥10) on admission and poor functional outcome (modified Rankin scale 4–6) at discharge were investigated using a logistic regression analysis.

Results—Neurological deficits on admission were less severe, and functional outcome at discharge was more favorable as the PT-INR level on admission increased. The multivariate analysis revealed that severe neurological deficits were inversely associated with PT-INR on admission (PT-INR 1.50–1.99: odds ratio, 0.66; 95% confidence interval, 0.43–1.00; PT-INR ≥2.00: odds ratio, 0.41; 95% confidence interval, 0.20–0.83; compared with a reference group of PT-INR <1.50). Poor functional outcome was less likely in patients with PT-INR ≥2.00 (odds ratio, 0.20; 95% confidence interval, 0.06–0.55) after adjustment for confounders.

Conclusions—Prestroke PT-INR ≥2.0 is associated with favorable clinical outcomes after acute cardioembolic stroke. *(Stroke. 2013;44:00-00.)*

Key Words: anticoagulation ■ clinical outcome ■ ischemic stroke ■ prothrombin time–international normalized ratio ■ warfarin

Among all subtypes of ischemic stroke, cardioembolic stroke causes the most severe neurological deficits. Patients who experience cardioembolic stroke are at significant risk of becoming bedridden or dying. Atrial fibrillation (AF) is the major cause of cardioembolic stroke.1 Because the prevalence of AF increases with age,2 one of the important issues in aging societies is to reduce the incidence of cardioembolic stroke. A randomized controlled trial showed that warfarin anticoagulation therapy can reduce the incidence of thromboembolism in patients with AF.3 In addition to stroke prevention, chronic anticoagulation therapy might result in less severe neurological symptoms in patients with AF who do experience cardioembolic stroke. Several retrospective studies have shown that efficient anticoagulation therapy (ie, prothrombin time–international normalized ratio [PT-INR] ≥2.0 on admission) reduced the risk of severe ischemic stroke4 and disability at discharge or at hospital death compared with patients who did not receive anticoagulation therapy.5,6 However, the relationship between preadmission intensity of anticoagulation and stroke severity on admission or at discharge remains controversial.7,8 The intensity of PT-INR recommended for Japanese patients with AF who were ≥70 years is lower (1.6–2.6) than those of other countries.9 Accordingly, Japanese patients are mostly not treated in the internationally recommended PT-INR target.
range (2.0–3.0). The goal of the present study was to clarify whether low PT-INR at the time of stroke onset is associated with the severity of neurological deficits and functional outcomes in Japanese patients with cardioembolic stroke.

**Methods**

**Study Subjects**

The Fukuoka Stroke Registry is a multicenter, hospital-based registry of patients with acute stroke. Ischemic stroke was classified into cardioembolic stroke, lacunar infarction, atherothrombotic infarction, and unclassified infarction as described. The patients who had been admitted to one of the participating hospitals within 24 hours after onset and who had a definite cardioembolic stroke were included in this study. Among them, the cases of 602 patients who were taking warfarin at the time of stroke onset were analyzed in the present study.

**Clinical Assessment**

We defined clinical characteristics such as risk factors, ischemic heart disease, chronic kidney disease, and cardiac diseases causing stroke as described in the online-only Data Supplement. PT-INR was measured on admission, and patients were classified into 3 groups according to the intensity of anticoagulation with warfarin: PT-INR <1.50, PT-INR 1.50 to 1.99, and PT-INR ≥2.00.

**Study Outcomes**

Neurological severity on admission was determined by the National Institutes of Health Stroke Scale (NIHSS) score. Severe neurological deficit on admission was defined as NIHSS ≥10. Functional disability was determined by the modified Rankin Scale (mRS) score at discharge. A poor functional outcome was defined as severe disability at discharge (mRS of 4 or 5) or in-hospital mortality (mRS of 6). The mean duration of hospitalization was 30 days (SD, 24 days).

**Statistical Analysis**

Clinical characteristics and clinical outcomes were compared among the 3 PT-INR categories by logistic regression analysis or by analysis of variance, as appropriate. Age-, sex-, and multivariate-adjusted odds ratios and 95% confidence intervals for each study outcome were estimated by logistic regression analysis. The multivariate model is described in the online-only Data Supplement. P values <0.05 were considered significant.

**Results**

**Clinical Characteristics of Patients**

Table 1 shows the clinical characteristics of the 602 subjects. The median value of PT-INR on admission was 1.32 (interquartile range, 1.12–1.60). The mean age was significantly younger, and the mean estimated glomerular filtration rate was significantly lower in the 45 patients with PT-INR ≥2.0 compared with the 411 patients with PT-INR <1.50. The frequency of valvular heart disease and that of previous ischemic stroke were progressively higher as the PT-INR level increased. No significant difference was found on preadmission mRS values among the 3 PT-INR categories. After admission, anticoagulation therapy was resumed with warfarin in 485 patients and with dabigatran in 9 patients. Among them, heparin bridging was performed in 453 patients. Gastrointestinal bleeding occurred in 11 patients with PT-INR <2.0, whereas no patients with PT-INR ≥2.0 developed it. Hemorrhagic conversion was observed in 167 patients (28%); among them, symptomatic hemorrhagic infarction occurred in 27 patients with PT-INR <2.0 and in 1 patient with PT-INR ≥2.0.

**Table 1. Clinical Characteristics According to PT-INR on Admission**

<table>
<thead>
<tr>
<th>PT-INR on Admission</th>
<th>N=602</th>
<th>n=411</th>
<th>n=146</th>
<th>n=45</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>&lt;1.50</td>
<td>1.50–1.99</td>
<td>≥2.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y; mean±SD</td>
<td>76.1±9.3</td>
<td>76.7±9.4</td>
<td>75.5±8.1</td>
<td>72.7±11.2*</td>
<td>0.005</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>326 (54)</td>
<td>220 (54)</td>
<td>77 (53)</td>
<td>29 (64)</td>
<td>0.34</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>437 (73)</td>
<td>288 (70)</td>
<td>121 (83)*</td>
<td>28 (62)</td>
<td>0.40</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>161 (27)</td>
<td>107 (26)</td>
<td>47 (32)</td>
<td>7 (16)</td>
<td>0.75</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>169 (28)</td>
<td>99 (24)</td>
<td>59 (40)*</td>
<td>11 (24)</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>556 (92)</td>
<td>386 (94)</td>
<td>126 (86)*</td>
<td>44 (98)</td>
<td>0.33</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>126 (21)</td>
<td>86 (21)</td>
<td>34 (23)</td>
<td>6 (13)</td>
<td>0.59</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>290 (48)</td>
<td>193 (47)</td>
<td>71 (49)</td>
<td>26 (58)</td>
<td>0.21</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²; mean±SD</td>
<td>61.1±22.6</td>
<td>61.9±23.2</td>
<td>61.1±21.1</td>
<td>53.2±20.1*</td>
<td>0.04</td>
</tr>
<tr>
<td>Valvular heart disease, n (%)</td>
<td>65 (11)</td>
<td>28 (7)</td>
<td>28 (19)*</td>
<td>9 (20)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sick sinus syndrome, n (%)</td>
<td>40 (7)</td>
<td>25 (6)</td>
<td>9 (6)</td>
<td>6 (13)</td>
<td>0.17</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>54 (9)</td>
<td>38 (9)</td>
<td>13 (9)</td>
<td>3 (7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Dilated cardiomyopathy, n (%)</td>
<td>5 (0.8)</td>
<td>4 (1)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0.98</td>
</tr>
<tr>
<td>Previous ischemic stroke, n (%)</td>
<td>270 (45)</td>
<td>166 (40)</td>
<td>78 (53)*</td>
<td>26 (58)*</td>
<td>0.002</td>
</tr>
<tr>
<td>Antiplalet therapy, n (%)</td>
<td>178 (30)</td>
<td>108 (26)</td>
<td>52 (36)*</td>
<td>18 (40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preadmission mRS, median (IQR)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*eGFR indicates estimated glomerular filtration rate; IQR, interquartile range; mRS, modified Rankin scale; and PT-INR, prothrombin time–international normalized ratio.*

*P<0.05 vs PT-INR<1.50.*
PT-INR and Clinical Outcomes

The admission NIHSS scores (Table 2) and discharge mRS values (Table 3) decreased as the PT-INR level increased. The proportion of severe neurological deficits on admission was significantly lower in the patients with PT-INR ≥1.50 compared with those with PT-INR <1.50 (Table 2). This trend did not change after adjusting for possible confounding factors (Table 2). The risk of poor functional outcome was lower in the patients with PT-INR ≥2.00 on admission compared with those with PT-INR <1.50 (Table 3). The probability of in-hospital mortality was lower in the patients with PT-INR 1.50 to 1.99 than in those with PT-INR <1.50, but this difference did not reach the level of significance. No deaths occurred among the patients with PT-INR ≥2.00 during the study period (Table I in the online-only Data Supplement).

Discussion

The present findings demonstrated that the intensity of warfarin anticoagulation at the onset of cardioembolic stroke is correlated with the clinical outcome. Specifically, the PT-INR is inversely correlated with the severity of neurological deficits and directly correlated with functional outcome. A PT-INR ≥1.50 at the onset of cardioembolic stroke was associated with a reduced risk of severe neurological deficits, and a PT-INR ≥2.00 was associated with a reduced risk of poor functional outcome at discharge.

Hylek et al5 were the first to report that effective anticoagulation was associated with decreased risks of disability and 30-day mortality after ischemic stroke compared with patients who received neither antiplatelet nor anticoagulation therapy. Comparable findings were obtained from the Registry of the Canadian Stroke Network. It was suggested that therapeutic anticoagulation before admission to the hospital for stroke was associated with a reduced probability of neurological severity on admission and with reduced disability or death at discharge.4 However, other research groups reported that preadmission anticoagulation was not associated with neurological severity at onset but was associated with a reduced risk of poor outcome,7 or that no correlation was found between previous use of antithrombotic agents and outcomes.8 In the present study, a PT-INR ≥2.00 at onset was associated with neurological symptoms and poor functional outcome when a cardioembolic stroke occurred. These observations support the notion that PT-INR of 2.00 alleviates the severity of neurological deficits and improves the functional outcome in patients who experience a cardioembolic stroke. Major bleeding rarely occurred in patients with PT-INR ≥2.0 in this cohort; however, a recent study suggested that the risk of major bleeding increases with an elevation of PT-INR.9 Although the incidence of bleeding increases with higher PT-INR, prestroke PT-INR ≥2.0 was associated with poststroke favorable outcomes.

Another study reported that the resolution of thrombus was observed during therapeutic anticoagulation in patients with deep vein thrombosis.10 Ay et al14 reported that patients with therapeutic anticoagulation had smaller infarcts compared with patients who were not receiving warfarin. Furthermore, the patients’ preadmission PT-INR values were inversely correlated with the lesion volume on diffusion-weighted MRI. Acceleration of thrombolysis by warfarin is probably mediated by inhibition of the thrombotic system and subsequent predominance of the fibrinolytic system.15 Therefore, therapeutic anticoagulation with warfarin may result in the formation of

Table 2. Relationship Between PT-INR on Admission and Severity of Neurological Deficits

<table>
<thead>
<tr>
<th>PT-INR</th>
<th>Admission NIHSS, Median (IQR)</th>
<th>No. of Patients With Severe Neurological Deficits/Total Patients (%)</th>
<th>Age- and Sex-Adjusted</th>
<th>Multivariate-Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR 95% CI P Value</td>
<td>OR 95% CI P Value</td>
</tr>
<tr>
<td>&lt;1.50</td>
<td>11 (4–18)</td>
<td>222/411 (54)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1.50–1.99</td>
<td>8 (2–16)</td>
<td>59/146 (40)</td>
<td>0.58</td>
<td>0.39–0.86 0.006</td>
</tr>
<tr>
<td>≥2.00</td>
<td>6 (4–13)</td>
<td>14/45 (32)</td>
<td>0.45</td>
<td>0.22–0.87 0.02</td>
</tr>
</tbody>
</table>

P for trend 0.003 <0.001 0.001 0.003

Severe neurological deficits were defined as baseline NIHSS ≥10. CI indicates confidence interval; IQR, interquartile range; mRS, the National Institutes of Health Stroke Scale; OR, odds ratio; and PT-INR, prothrombin time–international normalized ratio.

Table 3. Relationship Between PT-INR on Admission and Functional Outcome

<table>
<thead>
<tr>
<th>PT-INR</th>
<th>Discharge mRS, Median (IQR)</th>
<th>No. of Patients With Poor Functional Outcome/Total Patients (%)</th>
<th>Age- and Sex-Adjusted</th>
<th>Multivariate-Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR 95% CI P Value</td>
<td>OR 95% CI P Value</td>
</tr>
<tr>
<td>&lt;1.50</td>
<td>4 (1–5)</td>
<td>213/411 (52)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1.50–1.99</td>
<td>3 (1–5)</td>
<td>64/146 (44)</td>
<td>0.76</td>
<td>0.51–1.14 0.19</td>
</tr>
<tr>
<td>≥2.00</td>
<td>2 (1–4)</td>
<td>11/45 (24)</td>
<td>0.35</td>
<td>0.16–0.72 0.004</td>
</tr>
</tbody>
</table>

P for trend <0.001 <0.001 0.004 0.001

Poor functional outcome was defined as mRS ≥4 at discharge. CI indicates confidence interval; IQR, interquartile range; mRS, modified Rankin scale; OR, odds ratio; and PT-INR, prothrombin time–international normalized ratio.
smaller thrombi or a more fragile embolus that tends to spontaneously collapse at the site of occlusion, thereby leading to earlier recanalization. These mechanisms may contribute to the improved clinical outcomes.

Although we investigated a large number of patients, this study has some limitations. The study was hospital-based, and patients with either a minor stroke or sudden death related to stroke may have been excluded, thereby leading to selection bias. Of note, the frequency of patients with a PT-INR ≥2.00 (7%) was much lower in this study than in the previous studies (32%–55%). In the present study, low PT-INR values were attributable to low-dose warfarin prescribed in 89% of the subjects. The nationwide registry of Japanese patients with AF revealed that only 38% had PT-INR values ≥2.00, suggesting that anticoagulation therapy is insufficiently performed for patients with AF in Japan. To determine the association between PT-INR ≥2.00 and clinical outcomes with sufficient statistical power, more patients must be studied. Finally, patients with stroke in Japan are hospitalized for a long time, which may also have affected the clinical outcomes.

Acknowledgments
The authors thank the clinical research coordinators for their help in obtaining informed consent and collecting clinical data.

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Disclosures
None.

References
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Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Intensity of anticoagulation and clinical outcomes in acute cardioembolic stroke: the Fukuoka Stroke Registry
Supplemental Methods

Study subjects
Kyushu University Hospital and six other stroke centers participated in the Fukuoka Stroke Registry (FSR). The study design was approved by the institutional review boards and ethics committees of all seven hospitals. Stroke was defined as the sudden onset of a non-convulsive, focal neurological deficit persisting for more than 24 hours. A total of 10,394 patients who experienced a stroke or transient ischemic attack and were admitted to one of the participating hospitals within 24 hours after onset were recruited between June 1999 and March 2012. Among them, 2,765 patients were diagnosed with cardioembolic stroke. After we excluded 2,112 patients who were not taking warfarin at the time of stroke onset and 51 patients with no prothrombin time-international normalized ratio (PT-INR) data, the cases of 602 patients remained and were analyzed in the present study.

Clinical assessment
Hypertension was defined as systolic blood pressure $\geq 140$ mmHg or diastolic pressure $\geq 90$ mmHg in the chronic stage or as preadmission treatment with antihypertensive drugs. Diabetes mellitus was defined according to the diagnostic criteria of the Japan Diabetes Society in the chronic stage or based on a medical history of diabetes. Dyslipidemia was defined as a low-density lipoprotein-cholesterol level $\geq 3.62$ mmol/L, high-density lipoprotein-cholesterol level $<1.03$ mmol/L, triglycerides $\geq 1.69$ mmol/L, or preadmission treatment with a lipid-lowering drug. Atrial fibrillation was diagnosed based on electrocardiographic findings on admission or during hospitalization. Renal function was evaluated using the estimated glomerular filtration rate (eGFR), and chronic kidney disease was diagnosed when the patients had a low eGFR ($<60$ mL/min/1.73 m$^3$) on admission. eGFR was calculated using the equation proposed by the Japanese Society of Nephrology:

$$\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{serum creatinine (sCr)}^{-1.094} \times \text{age}^{-0.287} \text{ in males and eGFR (mL/min/1.73 m}^2) = 194 \times \text{sCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739 \text{ in females.}$$

Valvular heart disease included mitral stenosis and mitral or aortic valve replacement. Gastrointestinal bleeding was defined as any episodes of hematemesis or melena during hospitalization. Hemorrhagic conversion was defined as obvious hemorrhage detected by computed tomography. Symptomatic hemorrhagic infarction was defined as hemorrhagic conversion temporally and causally associated with the neurological deterioration of the patients’ clinical condition.

Statistical analysis
The multivariate model for neurological deficits included age, sex, prior ischemic stroke,
hypertension, diabetes mellitus, dyslipidemia, valvular heart disease, estimated glomerular filtration rate, antiplatelet therapy, and preadmission modified Rankin Scale. Thrombolysis and the National Institutes of Health Stroke Scale score on admission were also included in the model for functional outcome and in-hospital mortality. Statistical analyses were performed using the JMP version 9 software program (SAS Institute, Inc., Cary, NC, USA).

_Fukuoka Stroke Registry (FSR) Investigators_

The following hospitals participated in the Fukuoka Stroke Registry (FSR):

- Kyushu University Hospital
- National Hospital Organization Kyushu Medical Center
- National Hospital Organization Fukuoka Higashi Medical Center
- Fukuoka Red Cross Hospital
- St. Mary’s Hospital
- Steel Memorial Yawata Hospital
- Japan Labour Health and Welfare Organization Kyushu Rosai Hospital

The Steering Committee consisted of:

- Takao Ishitsuka, MD; Shigeru Fujimoto, MD: Department of Cerebrovascular Disease, Steel Memorial Yawata Hospital
- Setsuro Ibayashi, MD; Kenji Kusuda, MD: Department of Medicine, Seiai Rehabilitation Hospital
- Shuji Arakawa, MD: Department of Cerebrovascular Disease, Japan Labour Health and Welfare Organization Kyushu Rosai Hospital
- Katsumi Irie, MD: Department of Cerebrovascular Disease, Hakujuji Hospital
- Kenichiro Fujii, MD: Department of Cerebrovascular Disease, Fukuoka Red Cross Hospital
- Yasushi Okada, MD; Masahiro Yasaka, MD: Department of Cerebrovascular Disease and Clinical Research Institute, National Hospital Organization Kyushu Medical Center
- Tetsuhiko Nagao, MD: Midorinoclinic
- Hiroaki Ooboshi, MD: Department of Internal Medicine, Fukuoka Dental Collage
- Tsuyoshi Omae, MD: Department of Medicine, Imazu Red Cross Hospital
- Kazunori Toyoda, MD: Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center
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Kenji Fukuda, MD: Department of Internal Medicine, Division of Cardio-Vascular Medicine, Kurume University
Yoshihisa Fukushima, MD: Department of Cerebrovascular Disease, St. Mary’s Hospital
Kinya Tamaki, MD; Seizo Sadoshima, MD: Shinyoshizuka Hospital
### Supplemental Table I. Relationship between PT-INR on admission and in-hospital mortality

<table>
<thead>
<tr>
<th>PT-INR</th>
<th>Number of patients with IHM / total patients (%)</th>
<th>Age- and sex-adjusted</th>
<th>Multivariate-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>PT-INR &lt;1.50</td>
<td>42/ 411 (10)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>PT-INR 1.50–1.99</td>
<td>9/ 146 (6)</td>
<td>0.60</td>
<td>0.27–1.22</td>
</tr>
<tr>
<td>PT-INR ≥2.00</td>
<td>0 / 45 (0)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.01</td>
<td></td>
<td>–</td>
</tr>
</tbody>
</table>

IHM: In-hospital mortality, defined as death from all causes during hospitalization. OR: odds ratio, CI: confidence interval.