Low-Dose Aspirin for Prevention of Stroke in Low-Risk Patients With Atrial Fibrillation
Japan Atrial Fibrillation Stroke Trial

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Background and Purpose—Although the efficacy of anticoagulant therapy for primary prevention of stroke in patients with nonvalvular atrial fibrillation (NVAF) has been established, efficacy of antiplatelet therapy for low-risk patients is disputable in Japanese patients because of the frequent hemorrhagic complications. We examined the efficacy and safety of aspirin therapy in Japanese patients with NVAF in a prospective randomized multicenter trial.

Methods—Patients with NVAF were randomized to an aspirin group (aspirin at 150 to 200 mg per day) or a control group without antiplatelet or anticoagulant therapy. Primary end points included cardiovascular death, symptomatic brain infarction, or transient ischemic attack.

Results—A total of 426 patients were randomized to aspirin group and 445 to no treatment. The trial was stopped earlier because there were 27 primary end point events (3.1% per year; 95% CI, 2.1% to 4.6% per year) in the aspirin group versus 23 (2.4% per year; 95% CI, 1.5% to 3.5% per year) in the control group, suggesting a low possibility of superiority of the aspirin treatment for prevention of the primary end point. In addition, treatment with aspirin caused a marginally increased risk of major bleeding (7 patients; 1.6%) compared with the control group (2 patients; 0.4%; Fisher exact test $P = 0.101$).

Conclusions—For prevention of stroke in patients with NVAF, aspirin at 150 to 200 mg per day does not seem to be either effective or safe. Further prospective studies are needed to determine the best preventive therapy for cerebrovascular events in Japanese patients with NVAF. (*Stroke.* 2006;37:447-451.)

Key Words: aspirin ■ stroke ■ thrombosis

The efficacy of anticoagulant therapy has long been established for the primary prevention of stroke and transient ischemic attacks (TIAs) in patients with nonvalvular atrial fibrillation (NVAF).1–4 Despite conclusive evidence of efficacy, several studies have shown that use of warfarin in patients with atrial fibrillation (AF) is suboptimal.5 Indeed, antithrombotic therapy is not commonly given to Japanese NVAF patients (8%), probably because of the risk of critical bleeding during treatment.6 Instead, antiplatelet therapy (45%) or nontreatment (47%) are often selected to manage patients with NVAF,6 although little information is available about benefits and risks of aspirin treatment. Furthermore,
despite the fact that a high dose of aspirin (325 mg per day) but not a low dose (75 mg per day) has been shown to be effective for prevention of stroke,7,8 the majority of Japanese patients with NVAF are administered a low dose of aspirin (81 mg per day).9 The rationale for use of low-dose aspirin in Japanese patients is based on the risk of gastrointestinal intolerance and the dose-dependent risk of bleeding.10 In the present study, we aimed to examine the efficacy of low-dose aspirin for improving the prognosis of low-risk NVAF patients in a prospective randomized multicenter trial.

Methods

Patients

The Japan Atrial Fibrillation Stroke Trial (JAST) was performed at 13 centers and 76 affiliated hospitals in Japan. The protocol was approved by the institutional review board or ethics committee at each participating center or hospital, and written informed consent was given by each patient. Patients with chronic or intermittent AF documented by ECG at least twice within 12 months were candidates for this trial. Patients were excluded from the study if they met the following criteria: prosthetic heart valve, rheumatic heart disease, mitral valve disease, uncontrolled hypertension, hyperthyroidism, severe heart failure (New York Heart Association class IV), and a past history of symptomatic thromboembolic disease within a year, previous intracranial bleeding, or gastrointestinal hemorrhage within 6 months. Patients with other indications for anticoagulant therapy or antiplatelet agents were also excluded (ie, coronary artery disease, pulmonary embolization, venous thrombosis, and other diseases that the attending physician considered to be treated with these medicines). Furthermore, patients whose attending physicians considered it inappropriate for them to join the study were excluded. Patients with a history of stroke or TIA>1 year previously were exceptionally eligible if both the patient and physician agreed.

Design

The patients were randomly divided into 2 groups (ie, an aspirin group that received aspirin therapy [150 to 200 mg per day], and a control group that was not prescribed aspirin). Randomization was performed at 13 centers following instruction sheets sent from the executive office in Osaka University, and the randomized sequence was blocked from previewing by the investigators and the attending physician. The dose of aspirin was selected by the attending physician and also depending on the aspirin formulation available at each hospital. Patients were instructed to take aspirin every morning after breakfast. Treatment with 330 mg of aspirin on alternative days was also permitted. If patients taking anticoagulant or antiplatelet medicine were permitted to attend the study, they were required to discontinue their treatment for ≥2 weeks before randomization. Medication compliance was examined by physician’s questioning at every visit to clinic. Compliance was defined as good when patients took aspirin more than two thirds of prescribed aspirin. Sporadic use of aspirin and nonsteroidal anti-inflammatory agents was discouraged. Other medications were not prohibited during this trial.

Primary end points included cardiovascular death, symptomatic brain infarction, or TIA, whereas the secondary end points included noncardiovascular death, intracranial hemorrhage, major bleeding, and peripheral embolization. The criteria for cerebrovascular events were confirmed clinical signs of an acute-onset neurological deficit of presumed vascular origin. A TIA was defined as focal symptoms lasting for <24 hours. Patients with stroke events were evaluated by expert physicians (stroke specialists) at the periodical meetings of the event monitoring committee and the end points were assessed by investigators who had no knowledge of each patient’s treatment. Stroke, TIA, and intracranial bleeding were confirmed by computed tomography scanning or MRI in addition to the clinical data collected by the event monitoring committee. Subtypes of the cerebral infarction were also diagnosed by the committee according to the popularly used definitions.11,12 The final diagnosis of the subtypes of stroke was made by consensus. Major bleeding was defined as fatal bleeding, bleeding needed for hospital admission for treatment, blood transfusion, or a decrease of hemoglobin concentration >4 g/dL. Initially, a sample size of 754 per group was estimated to be necessary on the basis of an anticipated event rate for the primary end points of 3% per year in the control group and 1.5% per year in the aspirin group, with an 80% power of test and a 2-sided significance of P<0.05. However, because the number of patients registered was smaller than expected, the sample size was reduced to 492 per group, and instead, the mean follow-up period was extended from 2 to 3 years at the steering committee meeting, held September 13, 2000.

To ensure the safety of the trial, informal interim analyses of the event rate for both primary and secondary end points were performed every 6 months by a data and safety monitoring committee after ≥75% of the target number of patients had been registered. The data and safety monitoring committee was established to recommend early termination of the trial if it observed a clinically important treatment effect, unpredictable side effects, or a futile data for continuation. No formal rules for stopping the trial were adopted before the initiation of enrollment.

Laboratory Methods

Routine blood examination was performed before, 3 months, and every year after the entry. Plasma thrombin–antithrombin complex (TAT) levels were determined using the enzyme immunosassay TAT[S] (SRL, Inc), and D-dimer levels were determined using a latex agglutination test (COBAS reagent d-dimer; Roche Diagnostics K.K.). These assays allowed measurement of plasma TAT and D-dimer levels to a minimum of 1.0 ng/mL and 0.10 µg/mL, respectively. Plasma fibrinogen levels were assayed by the Clauss methods with a Sysmex CA-7000 coagulometer and the appropriate reagents and standards. The lower detection limit of this test was 20 mg/dL. Laboratory analyses were done in a blinded fashion. After determination of the baseline concentrations of TAT, D-dimer, and fibrinogen, the study population was divided into quartiles with an equal number of patients (TAT: first quartile <1.20 ng/mL; second quartile from 1.20 to 1.90 ng/mL; third quartile from 1.90 to 2.70 ng/mL; and fourth quartile ≥2.70 ng/mL; D-dimer: first quartile <170 ng/mL; second quartile from 170 to 400 ng/mL; third quartile from 400 to 600 ng/mL; and fourth quartile ≥600 ng/mL; fibrinogen: first quartile <234 mg/dL; second quartile from 244 to 282 mg/dL; third quartile from 282 to 328 mg/dL; and fourth quartile ≥328 mg/dL).

Statistical Analysis

All analyses were performed on an intent-to-treat basis. Differences of continuous variables between the 2 treatment groups were determined by the t test. Categorical variables were compared by the χ² test. In the case of low cell count (<5), Fisher exact test was used instead of the χ² test. In the interim analyses, the binomial probability was computed to examine the possibility of overturning a trend shown by the interim analysis. CIs for event rates were computed using a Poisson distribution. Survival curves were constructed by the Kaplan–Meier method, and differences in survival were assessed using the log-rank test. Multivariate logistic regression analysis was used to determine factors associated with primary end points. Aspirin treatment, age ≥75 years, gender, paroxysmal AF, systemic hypertension, hyperlipidemia, heart failure, smoking status, diabetes mellitus, previous cerebrovascular disease, D-dimer highest quartile, TAT highest quartile, and fibrinogen highest quartile were included as parameters. For all analyses, significance was defined as P<0.05 (2-sided).

Results

Randomization was started on September 1, 1998, and the study was stopped early based on the recommendation of the data and safety monitoring committee on May 31, 2002. This decision was made because of the following results of interim
analysis: (1) treatment with aspirin caused a marginally higher risk of major bleeding, and (2) aspirin therapy was unlikely (0.015%) to be superior to no treatment for prevention of both the primary and secondary end points. At the time of early termination, 907 patients had been entered into the study. Among them, 36 patients were excluded because of failure to fulfill the enrollment criteria or other administrative reasons. Accordingly, 871 patients were randomized to the open-label treatment, including 426 in the aspirin group and 445 in the group without treatment (Figure 1). During follow-up, 96 patients in the aspirin group and 89 patients in the control group were withdrawn from the study. However, the period before withdrawal was included in the analysis. Consequently, the mean follow-up period was 768±403 days (median 810 days; range 15 to 1365 days). The baseline characteristics of the 2 groups were similar (Table 1), with little difference of important prognostic variables such as age, hypertension, heart failure, and previous history of warfarin treatment.

Effect of Aspirin on the End Points

Eighty-four percent of the patients in the aspirin group took aspirin regularly. When the study was terminated, there had been 27 primary end point events (3.1% per year; 95% CI, 2.1% to 4.6% per year) in the aspirin group versus 23 (2.4% per year, 95% CI, 1.5% to 3.5% per year) in the control group according to the intention-to-treat analysis, and this represents a 50% increase in the risk of primary end points (95% CI, 0.85% to 2.70%; \(P=0.175\)) in patients assigned to aspirin after adjusting for age, gender, paroxysmal AF, hypertension, hyperlipidemia, diabetes mellitus, smoking, previous cerebrovascular disease, heart failure, high TAT, high D-dimer, and high fibrinogen. Kaplan–Meier curves for the primary event-free rates in patients with or without aspirin treatment showed that this difference was not significant (\(P=0.310\); Figure 2a), and the frequency of each individual primary end point was not significantly different between the 2 groups (Table 2). Also combined end points of stroke and TIA did not differ between the groups.

Secondary end point events were observed in 14 patients from the aspirin group and 9 patients from the control group. The frequency of each individual end point was not significantly different (Table 2). However, treatment with aspirin caused a marginally higher risk of major bleeding (7 patients; 1.6%) compared with the control group (2 patients; 0.4%), although Fisher’s exact test did not show any statistical significance (\(P=0.101\)). Figure 2b shows the Kaplan–Meier curves for the event-free rate for combined primary and secondary end points in the aspirin group versus the control group (\(P=0.109\)). Treatment with aspirin led to a 42% increase in the risk of a combined end point events (95% CI, 0.85% to 2.40%; \(P=0.185\)) after adjusting for age, gender, paroxysmal AF, hypertension, hyperlipidemia, diabetes mellitus, smoking, previous cerebrovascular disease, heart failure, high TAT, high D-dimer, and high fibrinogen. Multivariate logistic regression analysis revealed that an age of ≥75 years, diabetes mellitus, and the highest TAT quartile were independent predictors of the primary end points (Table 3). In contrast, heart failure and hypertension were not independently associated with the primary end points.

Five of the 7 patients with major bleeding were elderly, but their mean age of 66.4±9.0 years was not different from that of the other 862 patients (65.1±10.8 years). Intracranial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aspirin (n=426)</th>
<th>Control (n=445)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>65.5</td>
<td>64.8</td>
<td>0.338</td>
</tr>
<tr>
<td>Men</td>
<td>71.1%</td>
<td>69.7%</td>
<td>0.636</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>44.6%</td>
<td>45.2%</td>
<td>0.866</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.6%</td>
<td>40.4%</td>
<td>0.264</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>23.9%</td>
<td>21.2%</td>
<td>0.349</td>
</tr>
<tr>
<td>Current smoker</td>
<td>27.3%</td>
<td>32.8%</td>
<td>0.115</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12.7%</td>
<td>15.3%</td>
<td>0.262</td>
</tr>
<tr>
<td>Previous cerebrovascular disease</td>
<td>2.6%</td>
<td>2.5%</td>
<td>0.917</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.3%</td>
<td>10.1%</td>
<td>0.355</td>
</tr>
<tr>
<td>High risk**</td>
<td>42.0%</td>
<td>47.7%</td>
<td>0.094</td>
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<tr>
<td>History of warfarin</td>
<td>7.0%</td>
<td>8.5%</td>
<td>0.410</td>
</tr>
<tr>
<td>TAT, ng/mL</td>
<td>3.2±5.1</td>
<td>3.3±5.6</td>
<td>0.726</td>
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<tr>
<td>D-dimer, ng/mL</td>
<td>1.1±6.1</td>
<td>1.0±5.3</td>
<td>0.747</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>289±66</td>
<td>292±72</td>
<td>0.559</td>
</tr>
</tbody>
</table>

*Defined as a documented fasting total cholesterol concentration >220 mg/dL, fasting triglyceride concentration >150 mg/dL, or antilipidemic therapy; **defined as patients with hypertension, previous cerebrovascular disease, or heart failure.

TABLE 1. Patient Characteristics

Figure 1. Patient flow chart.
bleeding was observed in 4 patients from the aspirin group (0.94%) and 2 patients from the control group (0.45%).

**Discussion**

The present study indicated that treatment with aspirin at 150 to 200 mg per day did not improve the prognosis of Japanese patients with NVAF. It was considered reasonable to terminate this study after the detection of observations indicating a very low possibility of aspirin being superior for prevention of the primary end point and a slightly higher risk of major bleeding in the aspirin group. The probability of the trial being able to show the superiority of aspirin treatment was extremely low, even if we assumed that the frequency of events was twice as high in the control group. Moreover, the risk of major bleeding in patients on aspirin treatment was higher than in the control. In fact, 1 more event in the aspirin group would have led to a significant difference.

In the present study, dividing the number of strokes and TIA with mean follow-up period, annual incidence of ischemic brain events was calculated as 2.8% in the aspirin group and 2.1% in the control group. These rates are low compared with previous trials and are equivalent to those in the ATRIA study. The relatively low rate of events in the participants might have masked a favorable antithrombotic effect of aspirin. Also, patient selection bias may have reduced the preventive effect of aspirin because relatively high-risk patients were included in this study. Patients with hypertension, heart failure, or previous cerebrovascular events, who are recommended to receive anticoagulant therapy in the American Heart Association (AHA)/The American College of Cardiology (ACC) guidelines, were not excluded from the study. Although these risk factors were not independent predictors of clinical events in this study, the ineffectiveness of aspirin in high-risk patients may possibly have masked its benefit for others. Third, the aspirin dosage used in this study was lower than that recommended in the AHA/ACC guidelines. Finally, a high prevalence of cardioembolic stroke in this study may have influenced the effect of aspirin (Table 2). Meta-analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) I to III clinical trials showed that 52% of the ischemic strokes observed during these trials were classified as cardioembolic, and that aspirin appears to primarily reduce noncardioembolic stroke in AF patients.

| TABLE 3. Multivariate Analyses of Factors Associated With Primary End Points |
|-------------------------------------------------|----------------|----------------|
| Characteristic                                 | Hazard Ratio (95% CI) | P Value |
| Aspirin treatment                              | 1.50 (0.84–2.70) | 0.175 |
| Age >75 years                                  | 2.06 (1.08–3.95) | 0.028 |
| Men                                            | 0.77 (0.37–1.67) | 0.521 |
| Paroxysmal AF                                  | 1.05 (0.56–1.84) | 0.954 |
| Systemic hypertension                          | 0.82 (0.44–1.52) | 0.524 |
| Hyperlipidemia                                 | 1.37 (0.71–2.64) | 0.353 |
| Heart failure                                  | 0.45 (0.14–1.49) | 0.191 |
| Current smoker                                 | 1.45 (0.71–2.95) | 0.310 |
| Diabetes mellitus                              | 2.46 (1.25–4.83) | 0.009 |
| Previous cerebrovascular disease               | 2.63 (0.89–8.09) | 0.091 |
| D-dimer highest quartile                       | 1.01 (0.52–1.97) | 0.968 |
| TAT highest quartile                           | 1.95 (1.06–3.56) | 0.031 |
| Fibrinogen highest quartile                    | 1.16 (0.61–2.22) | 0.644 |

*Fisher test; †includes 2 subdural bleedings, thalamic bleeding, subarachnoid bleeding, urinary tract bleeding, gastric bleeding, and respiratory bleeding; ‡include subarachnoid bleeding and thalamic bleeding.

**Figure 2.** Kaplan–Meier survival curves for primary end points (a) and for primary plus secondary end points (b). Treatment with aspirin was not superior to treatment without aspirin for primary end points (log-rank; $P=0.310$) and secondary end points (log-rank; $P=0.109$).
The absolute risk of stroke varies widely according to age and the presence of coexistent disease. Factors associated with stroke among participants in the SPAF I to III trials who received placebo or aspirin therapy have been reported previously, indicating that age, female sex, history of hypertension, systolic blood pressure, and previous stroke or TIA were independently associated with an increased risk of stroke. Multivariate analysis performed in this study showed that an age of >75 years, diabetes mellitus, and a TAT in the upper quartile were independently associated with an increase of primary end point events (Table 3).

A hypercoagulable state, including elevated levels of fibrinogen, d-dimer, and TAT, is often seen in patients with AF. However, it has not been clearly determined whether these coagulation markers are predictors of ischemic stroke. This study revealed that patients with a high TAT level may have a higher risk of primary end point events, although neither fibrinogen nor d-dimer was a predictor for unknown reasons.

Major bleeding complications, especially intracranial hemorrhage, are an important issue with respect to the prophylaxis of stroke in patients with NVAF. The incidence of major bleeding and intracranial hemorrhage was lower in the previous studies compared with the present study. The incidence of intracerebral hemorrhage was reported to be higher in Japan than in Western countries, so Japanese patients may be more prone to develop hemorrhagic events than Western patients. Indeed, intracerebral microbleeding is frequently observed by MRI in the upper quartile were independently associated with an increase of primary end point events (Table 3).

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The present study has some potential limitations. Because the design of the trial was not double-blind, we were not able to exclude the existence several biases. Also, the trial was terminated prematurely because of the risk of hemorrhage and the lack of demonstrable superiority of aspirin treatment. Although interim analysis was designed to ensure the safety of the study, multiple interim analyses may have influenced the results. The high incidence of major bleeding may depend on racial or ethnic differences.

For prevention of stroke in patients with NVAF, aspirin at 150 to 200 mg per day does not seem to be either effective or safe. Further prospective studies are needed to determine the best preventive therapy for cerebrovascular events in Japanese patients with NVAF.

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References

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