Aspirin for Stroke Prevention in Elderly Patients With Vascular Risk Factors
Japanese Primary Prevention Project

Shinichiro Uchiyama, MD; Naoki Ishizuka, PhD; Kazuyuki Shimada, MD; Tamio Teramoto, MD; Tsutomu Yamazaki, MD; Shinichi Oikawa, MD; Masahiro Sugawara, MD; Katsuyuki Ando, MD; Mitsu Murata, MD; Kenji Yokoyama, MD; Kazuo Minematsu, MD; Masayasu Matsumoto, MD; Yasuo Ikeda, MD; on behalf of the JPPP Study Group

Background and Purpose—The effect of aspirin in primary prevention of stroke is controversial among clinical trials conducted in Western countries, and no data are available for Asian populations with a high risk of intracranial hemorrhage. The objective of this study was to evaluate the effect of aspirin on the risk of stroke and intracranial hemorrhage in the Japanese Primary Prevention Project (JPPP).

Methods—A total of 14,464 patients (age, 60–85 years) with hypertension, dyslipidemia, and diabetes mellitus participated and were randomized into 2 treatment groups: 100 mg of aspirin or no aspirin. The median follow-up period was 5.02 years.

Results—The cumulative rate of fatal or nonfatal stroke was similar for the aspirin (2.068%; 95% confidence interval [CI], 1.750–2.443) and no aspirin (2.299%; 95% CI, 1.963–2.692) groups at 5 years; the estimated hazard ratio was 0.927 (95% CI, 0.741–1.160; P=0.509). Aspirin nonsignificantly reduced the risk of ischemic stroke or transient ischemic attack (hazard ratio, 0.783; 95% CI, 0.606–1.012; P=0.061) and nonsignificantly increased the risk of intracranial hemorrhage (hazard ratio, 1.463; 95% CI, 0.956–2.237; P=0.078). A Cox regression adjusted by the risk factors for all stroke, which were age >70 years, smoking, and diabetes mellitus, supported the above result.

Conclusions—Aspirin did not show any net benefit for the primary prevention of stroke in elderly Japanese patients with risk factors for stroke, whereas age >70 years, smoking, and diabetes mellitus were risk factors for stroke regardless of aspirin treatment.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00225849.

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Key Words: aspirin ■ diabetes mellitus ■ intracranial hemorrhage ■ risk factor ■ stroke prevention

Antiplatelet drugs are used for the secondary prevention of stroke because antiplatelet therapy has been proven to have a larger benefit than risk in this setting.1 For this purpose, aspirin is the most widely used antiplatelet drug worldwide, not only because of low cost but also because of huge experiences, equal efficacy in men and women, young and old patients, and diabetics and nondiabetics with predictive benefit/risk profile, and no dependency on (currently recognized) genetic underpinnings for efficacy.2,3 On the contrary, large clinical trials conducted in Western countries have reported conflicting results regarding the efficacy of aspirin for the primary prevention of stroke,4,7 and no evidence is available at http://stroke.ahajournals.org.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.012461/-/DC1.

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1605
available regarding the effect of aspirin in Asian populations, which have a higher risk of intracranial hemorrhage (ICH) than white populations. The Japanese Primary Prevention Project (JPPP) was an investigator-driven, nationwide, multicenter, open-label, randomized, parallel-group trial of aspirin for the primary prevention of vascular events, including stroke that was conducted in 14,464 Japanese patients who were ≥60 years old and had at least one major vascular risk factor. Patients were randomized to receive either 100 mg of aspirin or no aspirin and were followed for ≤6.5 years. The primary outcome was a composite of nonfatal myocardial infarction (MI), nonfatal stroke, and vascular death. The secondary outcomes included individual end points. The last follow-up examination was performed in May 2012, and the median follow-up period was 5.02 years.

JPPP was the first large randomized controlled trial of aspirin in an Asian population, which accounts for >60% of the world’s population, and was thus expected to make a great contribution to public health worldwide. The main results of the JPPP have recently been presented and published. Aspirin did not significantly reduce the composite primary outcome. Regarding the secondary outcomes, aspirin significantly reduced nonfatal MI and transient ischemic attack (TIA) but did not reduce nonfatal stroke and significantly increased extracranial hemorrhage.

The objective of this study was to evaluate the effects of aspirin on ischemic stroke and ICH for the primary prevention of stroke in more detail using an exploratory post hoc analysis of the patients who participated in the JPPP.

Methods
The details of the study design have been published previously. The JPPP was an investigator-driven, nationwide, multicenter cooperative, randomized, open-label, parallel-group clinical trial. Patients were recruited by their primary care physicians at 1,007 clinics across Japan between March 2005 and June 2007. The inclusion and exclusion criteria have been described elsewhere. Patients between the ages of 60 and 85 years and who had hypertension, dyslipidemia, and diabetes mellitus were included. All of these risk factors were diagnosed according to Japanese guideline criteria: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg for hypertension; total cholesterol ≥220 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, or triglyceride ≥150 mg/dL for dyslipidemia; and fasting plasma glucose ≥126 mg/dL, any blood glucose ≥200 mg/dL in the 75-g glucose tolerance test, or hemoglobin A1c 26.5% for diabetes mellitus. Patients with history of coronary artery disease, cerebrovascular disease, including TIA, atherosclerotic disease requiring surgery or intervention, or atrial fibrillation, were excluded. Patients with history of peptic ulcer or bleeding disorder were also excluded. Furthermore, patients with allergy or hypersensitivity to aspirin and those who were receiving other antiplatelet drugs or anticoagulants were also excluded.

Written informed consent was obtained from all the patients. The study was conducted according to the Declaration of Helsinki and Ethical Guidelines for Clinical Studies and was approved by the institutional review board of each participating center.

After a baseline evaluation, the patients were randomized 1:1 to receive either a 100-mg tablet of enteric-coated aspirin or no aspirin, in addition to any ongoing medication. The randomization was stratified according to the 3 risk factors, and 7 strata were used to account for all possible combinations. The minimization method was applied to balance sex and age within each stratum. Pseudorandom numbers were generated using the Mersenne Twister method with a seed of 4989. The study statistician generated the random allocation sequence using a central computerized system, and study physicians were informed of the treatment assignments via the study website or by fax. At baseline and at each annual study assessment, the following variables were evaluated in the clinic: disease outcomes, adverse events, adherence with treatment, blood pressure, serum lipids, blood glucose, smoking status, and body weight. Follow-up of the last recruited patient was completed in May 2012. Risk factor control was continued throughout the follow-up period according to the Japanese therapeutic guidelines.

The primary outcome was a composite of death from cardiovascular causes (MI, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal MI. Secondary end points were a composite of the same events as the primary end point plus TIA, angina pectoris, and atherosclerotic disease requiring surgery or intervention. Secondary end points were death from cardiovascular disease, death from noncardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal MI, TIA, angina pectoris, atherosclerotic disease requiring surgery or intervention, and serious extracranial hemorrhage requiring transfusion or hospitalization. Study end points were assessed centrally and biannually by an expert, multidisciplinary event adjudication committee that was blinded to the treatment assignments according to the Prospective Randomized Open Blinded End Point (PROBE) trial design.

Apart from the primary and secondary end points described earlier, we evaluated the effects of aspirin on fatal or nonfatal stroke, ischemic stroke plus TIA, ischemic stroke, and ICH using exploratory Cox regression analyses in this stroke substudy. The distribution of time-to-events was estimated using the Kaplan–Meier method in each study group. Intergroup differences in the events were assessed using the stratified log-rank test with stratification for risk factors and a 2-sided significance level of α=0.05. Hazard ratios (HRs) were calculated using the Cox proportional hazards model, and the 95% confidence intervals (CIs) were determined. Adjustments for factors used in the allocation of patients to the study groups were incorporated as needed. We also calculated the risk score for all stroke events using the Cox regression hazard model. Then, we performed a subgroup analysis on the effects of aspirin on risk of stroke and TIA by classifying the patients into high-risk and low-risk groups after scoring each risk factor based on the results of the Cox regression analysis.

Results
The percentages of vascular risk factors and variables of risk factors at baseline for the recruited patients are shown in Table 1; these results have already been reported in detail.

The details of cerebrovascular events are shown in Table 2. Fatal or nonfatal strokes occurred in 128 patients in both the aspirin and no aspirin groups. Significantly fewer patients experienced TIA before any stroke in the aspirin group than in the no aspirin group, as has already been reported. The cumulative rates of any stroke or TIA in both groups are shown in Figure 1A. No significant difference in the rate of any stroke or TIA at 5 years was observed between the 2 groups (2.068% in the aspirin group and 2.299% in the no aspirin group; adjusted HR, 0.927; 95% CI, 0.741–1.160; P=0.509).

Figure 1B shows the cumulative rates of any stroke in both groups. Furthermore, no significant difference in the rate of any stroke at 5 years was observed between the 2 groups (1.809% in the aspirin group and 1.828% in the no aspirin group; adjusted HR, 1.011; 95% CI, 0.791–1.291; P=0.932). Figure 1C shows the cumulative rates of ischemic stroke at 5 years in both groups. Fewer ischemic strokes occurred in the aspirin group than in the no aspirin group, but the difference was not significant (1.199% in the aspirin group and 1.451%
The details of ICH are shown in Table 2. Cerebral hemorrhage occurred more frequently in the aspirin group (28 patients) than in the no aspirin group (15 patients), whereas the rates of subarachnoid hemorrhage (10 and 8 patients, respectively) and subdural hematoma (13 and 12 patients, respectively) were comparable between the 2 groups. The cumulative rate of ICH at 5 years was nonsignificantly higher in the aspirin group than in the no aspirin group (0.748% in the aspirin group and 0.511% in the no aspirin group; adjusted HR, 1.463; 95% CI, 0.956–2.237; P=0.078; Figure 1D).

The factors affecting stroke and TIA were evaluated using a Cox regression analysis in all patients recruited (Table 3). Aspirin was not one of the factors affecting cerebrovascular events. Age ≥70 years, smoking, and diabetes mellitus were independent risk factors for cerebrovascular events. According to the estimated parameters, the risk score was calculated as a total of 2 for age ≥70 years, 1 for smoking, and 1 for diabetes mellitus. A score of 0 or 1 was classified as low risk, and a score of 2 or more was classified as high risk. The cumulative rate of cerebrovascular events at 5 years was not different between the aspirin group and the no aspirin group not only for the low-risk patients (1.154% in the aspirin group and 1.390% in the no aspirin group; HR, 0.839; 95% CI, 0.529–1.330%; P=0.4538), but also for the high-risk patients (2.722% in the aspirin group and 2.961% in the no aspirin group; HR, 0.955; 95% CI, 0.739–1.234; P=0.7246; Figure 2).

Discussion

Clinical trials in Western countries have reported conflicting results regarding the efficacy of aspirin for primary stroke prevention.7–6 According to a meta-analysis reported by the Antithrombotic Trialists’ Collaboration,7 aspirin did not reduce the risk of stroke for primary prevention because the risk ratio of stroke for aspirin versus a control was 0.95 (95% CI, 0.85–1.06). In this meta-analysis, aspirin nonsignificantly reduced the risk of ischemic stroke (rate ratio for aspirin versus control, 0.86; 95% CI, 0.74–1.00) but nonsignificantly increased the risk of hemorrhagic stroke (rate ratio, 1.32; 95% CI, 1.00–1.75).7 Results of our study were similar to these results. Therefore, the generalization of these results to the Japanese elderly population with risk factors for stroke seems reasonable, and aspirin can be concluded not to reduce the risk of stroke because the nonsignificant reduction of ischemic stroke is offset by the nonsignificant increase in hemorrhagic stroke. The presently ongoing Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE),12 A Study of Cardiovascular Events in Diabetes (ASCEND),13 Aspirin in Reducing Events in the Elderly (ASPREE),14 and International Standard Randomised Controlled Trial Number (ISRCTN)15 trials, in which the majority of recruited patients are from Western populations, may provide additional information regarding ethnic differences in the efficacy and safety of aspirin for the primary prevention of stroke.

Aspirin should be used for patients in whom a net clinical benefit, which is estimated by the total incidence of major ischemic and hemorrhagic events, can be expected.16–19 The rate of ischemic stroke is higher in Japan than in the United States and is comparable to that in Western Europe, whereas the rate of hemorrhagic stroke is higher than that in the populations of both the United States and Western Europe.8,20,21 Therefore, we suspected that the risk-benefit profile of aspirin for primary stroke prevention might be different between Japanese and Western populations. In reality, the rate of ischemic stroke was lower in the JPPP population than in the Antithrombotic Trialists’ Collaboration (ATT) population for

### Table 1. Baseline Characteristics and Risk Factor Profiles

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=7220)</th>
<th>No Aspirin (n=7244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>70.6 (6.2)</td>
<td>70.5 (6.2)</td>
</tr>
<tr>
<td>Men, number (%)</td>
<td>3055 (42.3%)</td>
<td>3068 (42.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6133 (84.9%)</td>
<td>6145 (84.8%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5198 (72.0%)</td>
<td>5200 (71.8%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2445 (33.9%)</td>
<td>2458 (33.9%)</td>
</tr>
<tr>
<td>Body mass index &gt;25 kg/m²</td>
<td>2644 (36.6%)</td>
<td>2604 (35.9%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>959 (13.3%)</td>
<td>934 (12.9%)</td>
</tr>
<tr>
<td>Family history</td>
<td>1981 (27.4%)</td>
<td>1982 (27.4%)</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>137.1 (15.8)</td>
<td>137.2 (15.6)</td>
</tr>
<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>77.7 (10.4)</td>
<td>77.6 (15.6)</td>
</tr>
<tr>
<td>TC, mean (SD), mg/dL</td>
<td>202.9 (32.9)</td>
<td>203.6 (32.5)</td>
</tr>
<tr>
<td>LDL, mean (SD), mg/dL</td>
<td>132.8 (76.0)</td>
<td>131.0 (75.9)</td>
</tr>
<tr>
<td>HDL, mean (SD), mg/dL</td>
<td>107.8 (31.2)</td>
<td>107.7 (32.0)</td>
</tr>
<tr>
<td>TG, mean (SD), mg/dL</td>
<td>132.8 (76.0)</td>
<td>131.0 (75.9)</td>
</tr>
<tr>
<td>FPG, mean (SD), mg/dL</td>
<td>107.8 (31.2)</td>
<td>107.7 (32.0)</td>
</tr>
<tr>
<td>HbA1c, mean (SD), %</td>
<td>6.1 (1.0)</td>
<td>6.0 (1.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>24.2 (3.5)</td>
<td>24.2 (3.4)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycohemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglycerides.

### Table 2. Cerebrovascular Events and Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Events</th>
<th>Aspirin</th>
<th>No Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular events</td>
<td>147</td>
<td>128</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>128</td>
<td>102</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>85</td>
<td>102</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td>Unclassified</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Other hemorrhage</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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primary prevention (0.26%/y versus 1.04%/y), whereas the rate of hemorrhagic stroke was higher in the JPPP population than in the ATT population (0.08%/y versus 0.03%/y). However, the results of our subanalysis of stroke in the JPPP were similar to the results of the meta-analysis reported by ATT regarding the net relative benefit for primary stroke prevention.

The cumulative rate of ICH at 5 years was 0.748% in the aspirin group and 0.511% in the no aspirin group. In JPPP population, the rate of hypertension was high, which was 85%, although the blood pressure was well controlled as a whole because the mean systolic blood pressure was 137 mmHg and the mean diastolic blood pressure was 78 mmHg at baseline. According to the results of Hisayama study, incidence of cerebral hemorrhage was 1.2/1000 person-year in persons with high normal blood pressure (130–139/85–89 mmHg). The estimated numbers in 7000 people at 5 years in one group of JPPP are calculated to be 42, which is comparable to 38 in the aspirin group and <23 in the no aspirin group. However, the data in Hisayama study was relatively old because they included 32-year-old data, when the incidence of cerebral hemorrhage was high. In Japan, the incidence of cerebral hemorrhage is gradually declining along with the progress of blood pressure management. According to recent stroke registries in Japan, percentage of hemorrhagic stroke is ≈25% of all strokes, which is still higher than the percentage in Western countries. In Hisayama study described earlier, the percentage of cerebral hemorrhage was 22% to 30% in people with high normal to grade 1 hypertension. In JPPP, the percentage of cerebral hemorrhage was 30% in the aspirin group and 23% in the no aspirin group. Taking together these data into consideration, the rate of ICH in JPPP population seems to be reasonable.

The relatively low rate of ischemic stroke may be attributable to well-controlled risk factors, as demonstrated in the baseline data. However, despite the sufficient

Table 3. Cox Regression to Calculate Risk Score for Cerebrovascular Events

<table>
<thead>
<tr>
<th>Factor</th>
<th>Parameter Estimate</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>−0.07906</td>
<td>0.489</td>
<td>0.924 (0.379–1.516)</td>
</tr>
<tr>
<td>Female</td>
<td>−0.21015</td>
<td>0.085</td>
<td>0.810 (0.638–1.029)</td>
</tr>
<tr>
<td>Age ≥70 y</td>
<td>0.79179</td>
<td>&lt;0.001</td>
<td>2.207 (1.718–2.836)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.4126</td>
<td>0.009</td>
<td>1.513 (1.111–2.061)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.44123</td>
<td>&lt;0.001</td>
<td>1.555 (1.237–1.954)</td>
</tr>
</tbody>
</table>

A Cox regression analysis to calculate the risk score for all the patients recruited in the JPPP showed that the risk factors for cerebrovascular events were age >70 years, smoking, and diabetes mellitus. Hypertension and dyslipidemia were common in both groups, which might have masked their significance as risk factors. The present results suggest that smoking cessation and the management of diabetes mellitus are important as modifiable risk factors to reduce the residual risk of cerebrovascular events, regardless of treatment with aspirin in elderly Japanese patients with vascular risk factors.

In limitation of this study, this was not a double-blind study but was a PROBE study. We think that there was no problem in selection bias. Because patients who were eligible at screening to meet inclusion but not exclusion criteria were recruited consecutively at each clinic, the study statistician generated random allocation sequence using a central computerized system, and study physicians were informed of treatment assignments via the study website as previously described. Baseline characteristics, which were reported in detail previously, were balanced between the 2 groups for patient demographics and disease risk factors. Additionally, adjudication of end points was performed centrally by an expert committee blinded to treatment assignment.

As described in the main analysis paper of JPPP, we used modified intention-to-treat analysis. We stated there in detail what kind of patients were included for this analysis. As for crossover to aspirin, we did not apply rank preserving structural failure time models to assume a difference from the case of 100% adherence. Because accuracy of information on adherence to aspirin was not sufficient to apply the models. Self-reported adherence to study medication at every year is shown in Table I in the online-only Data Supplement.

The number of patients lost to follow-up was 791 in the aspirin group and 753 in the no aspirin group as reported previously. It is likely that some strokes occurred among participants lost to follow-up. However, the potential effect of under-ascertainment is likely to be small as discussed previously.

Dose of aspirin we used was 100 mg in JPPP. One might argue the possibility that other doses could have a different behavior. However, clinical evidence suggested that the magnitude of the benefit of aspirin is similar for doses from 50 to 1500 mg. In contrast, toxicity does vary by dose; principal toxicity of aspirin is gastrointestinal hemorrhage, and higher doses of aspirin are associated with greater risk. Therefore, lower doses of aspirin (≤325 mg) are recommended for long-term prevention of vascular events.

JPPP was a collaborative study mainly not by vascular neurologists but by general physicians, and vascular imaging was not required for the diagnosis of stroke. Therefore, it was difficult to classify atherothrombotic stroke and lacunar stroke. However, there has been no clear evidence for the difference in the efficacy of antiplatelet therapy between atherothrombotic stroke and lacunar stroke to date. In reality, the American Heart Association/American Stroke Association Guidelines for stroke prevention in patients with stroke and TIA recommend antiplatelet therapy in noncardioembolic ischemic stroke, including not only atherothrombotic stroke but also lacunar stroke.

In conclusion, aspirin did not have any net benefit for the primary prevention of strokes in elderly Japanese patients with risk factors.
This study was presented in part before Late Breaking Science of the International Stroke Conference 2015 on February 12 in Nashville.

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Disclosures
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Meta-Analysis


References


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Supplementary Table 1. Adherence to test drug in aspirin and no aspirin groups

<table>
<thead>
<tr>
<th></th>
<th>Aspirin group</th>
<th>No aspirin group</th>
</tr>
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<tbody>
<tr>
<td>Year 1</td>
<td>6327/7118 (88.89%)</td>
<td>7050/7154 (98.55%)</td>
</tr>
<tr>
<td>Year 2</td>
<td>5918/6983 (84.75%)</td>
<td>6863/7042 (97.46%)</td>
</tr>
<tr>
<td>Year 3</td>
<td>5560/6819 (81.54%)</td>
<td>6507/6832 (95.24%)</td>
</tr>
<tr>
<td>Year 4</td>
<td>5265/6637 (79.33%)</td>
<td>6148/6684 (91.98%)</td>
</tr>
<tr>
<td>Year 5</td>
<td>3238/4263 (75.96%)</td>
<td>3857/4276 (90.20%)</td>
</tr>
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脳血管障害の危険因子を持つ高齢患者に対するアスピリンの脳卒中予防効果

Japanese Primary Prevention Project

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脳血管障害の危険因子を持つ高齢患者に対するアスピリンの脳卒中予防効果

背景および目的：欧米諸国で実施された臨床試験ではアスピリンの脳卒中一次予防効果に対する評価が定まっておらず、頭蓋内出血のリスクが高いアジア人についてのデータはない。日本のJapanese Primary Prevention Project（JPPP）の目的は脳卒中および頭蓋内出血のリスクに対するアスピリンの予防効果を評価することである。

方法：高血圧、脂質異常症、糖尿病を有する14,464例（60〜85歳）を対象に、無作為にアスピリン100mg投与群とアスピリン非投与群に分かれた。追跡期間の中央値は5.02年であった。

結果：致死性および非致死性脳卒中の5年間の累積発症率は、アスピリン投与群（2.08%、95%信頼区間（CI）：1.750〜2.443）とアスピリン非投与群（2.299、95% CI：1.963〜2.692）で差がなく、推定ハザード比は0.997（CI：0.741〜1.160、P = 0.509）であった。アスピリンによる虚血性脳卒中および一過性脳虚血発作のリスク低下は有意ではなく（ハザード比3.783、95% CI：0.606〜1.012、P = 0.061）。頭蓋内出血のリスク増加も有意ではなかった（ハザード比1.463、95% CI：0.956〜2.237、P = 0.078）。

結論：アスピリンは、脳卒中の危険因子を有する高齢日本人の一次予防において、有意な効果は認めなかった。70歳超の年齢、喫煙、糖尿病はアスピリンの投与に関係なく脳卒中の危険因子であった。

臨床試験登録情報：URL：http://www.clinicaltrials.gov。有効の識別番号：NCT00225849。

であり、世界的に公衆衛生に大きく貢献するものと期待された。JPPPの主な結果は最近公表され11,12.アスピリンによる複合主要評価項目の有意な減少は認められなかった。次回の評価においては、アスピリンは非致死性心筋梗塞と一過性脳虚血発作（TIA）を有意に減少させた。非致死性脳卒中の減少はみられず、頭蓋外出血に有意に増加した11.12.

本研究の目的は、JPPPに参加した患者の探索的その後解析により、脳卒中の一次予防として虚血性脳卒中およびICHに対するアスピリンの効果を詳細に解析することである。

### 方 法

本研究デザインの詳細は既報のとおりである11. JPPPは、医師主導の全国多施設共同、無作為化、非盲検、並行群間比較臨床試験である。患者の登録は2005年3月～2007年6月まで、全国1,007カ所のクリニックでプライマリケア科により実施された。選択基準と除外基準の詳細も既報のとおりである11.60～85歳で、高血圧、脂質異常症、糖尿病を有する患者が対象とされた。これらの危険因子はすべて日本のガイドライン基準に従って診断した（高血圧：収縮期血圧≧140 mmHgまたは拡張期血圧≧90 mmHg、脂質異常症：総コレステロール≧220 mg/dL、LDLコレステロール≧140 mg/dL、HDLコレステロール≧40 mg/dLまたは中性脂肪≧150 mg/dL、糖尿病：空腹時血糖値≧126 mg/dL、75 g プドウ糖負荷試験で血糖≧200 mg/dLまたはHbA1c≧6.5%11）に伴う動脈硬化症、TIAを含む脳血管疾患、手術や血管内治療を要するアテローム硬化性疾患、心房細動患者は除外した。また、消化性潰瘍または出血性疾患の既往がある患者、アスピリンに対するアレルギーまたは過敏症がある患者、その他の抗菌薬性薬や抗凝固薬を服用中の患者も除外した。すべての患者から直筆による同意書を取得した。本研究はヘルシンキ宣言および臨床研究に関する倫理指針に従って実施され、各参加施設の施設内倫理審査委員会に承認された。

ベースライン評価の後、患者は服用中の薬剤を継続したままアスピリン腸溶錠100 mgの投与または非投与のいずれかの群に1:1の比率で無作為に割り付けられた。無作為割り付けは3つの危険因子により層別化し、7層ですべての組み合わせを構成した。各層の性別と年齢のバランスをとるため最小化法を適用した。4,989のseedでMersenne Twister法により疑似乱数を生成した。統計担当者が中央のコンピュータシステムで無作為割り付け順序を作成し、治療の割り付けは本研究専用のウェブサイトまたはファックスで参加医師に伝えられた。ベースライン評価時と毎年の追跡調査の際には、イベントの発症状況、有害事象、治療に対するアドヒアランス、血管圧、血清脂質値、血糖、喫煙状況、体重を調べた。最後に登録した患者の追跡調査は2012年5月に終了した。日本全治療ガイドラインに従って、追跡期間中は危険因子のコントロールを継続した11,12.

主要評価項目は、心血管疾患に起因する死亡（心筋梗塞、脳卒中、その他の心血管疾患）、非致死性脳卒中（虚血性または出血性、不特定の脳血管イベントを含む）、非致死性心筋梗塞の複合項目とした。次回の評価項目は、主要評価項目と同じイベント+TIA、狭心症、手術または血管内治療を要するアテローム硬化性疾患の複合イベントとした。上記以外に、心血管疾患による死亡、心血管系以外の原因による死亡、非致死性脳卒中（虚血性または出血性）、非致死性心筋梗塞、TIA、狭心症、手術または血管内治療を要するアテローム硬化性疾患、輪血または入院を要する重篤な頭蓋外出血も次回の評価項目とした。これらのイベントの評価は、Prospective Randomized Open Blinded End Point（PROBE）試験デザインに従って、治療の割り付けを盲検化した専門の総合イベント判定委員会が中央で2回実施した。

上記の主要および次回の評価項目とは別に、この脳卒中サブスタディでは探索的Cox回帰分析により、致死性または非致死性脳卒中、虚血性脳卒中+TIA、虚血性脳卒中、ICHに対するアスピリンの効果を評価した。無イベント期間の分布は投与群ごとにKaplan-Meier法で推定した。イベントの群間差は、層別クラック検定により評価し、危険因子を層別化し両側有意水準α=0.05で判定した。ハザード比（HR）はCox比例ハザードモデルにより計算し、95%信頼区間（CI）を求めた。必要に応じて、被験者の投与群への割り付けに使用した因子の調整を行った。また、Cox回帰ハザードモデルで全脳卒中イベントのリスクスコアを計算し、その結果をもとに各危険因子をスコア化した後、リスク群と低リスク群に患者を分類し、脳卒中およびTIAのリスクに対するアスピリンの効果についてサブグループ解析を実施した。

### 結 果

ベースラインにおける2群の各危険因子の割合を表1に示す。これらの結論はすでに詳細に報告している。11.12.

脳血管イベントの詳細を表2に示す。致死性または非致死性脳卒中はアスピリン投与群、非投与群ともに128
脳血管障害の危険因子を持つ高齢患者に対するアスピリンの脳卒中予防効果

表1 ベースラインの特徴および危険因子のプロファイル

<table>
<thead>
<tr>
<th></th>
<th>アスピリン投与群 (n=7,220)</th>
<th>アスピリン非投与群 (n=7,244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>平均年齢（SD）、歳</td>
<td>70.6（6.2）</td>
<td>70.5（6.2）</td>
</tr>
<tr>
<td>男性率（％）</td>
<td>3,055（42.3％）</td>
<td>3,068（42.4％）</td>
</tr>
<tr>
<td>高血圧</td>
<td>6,133（84.9％）</td>
<td>6,145（84.8％）</td>
</tr>
<tr>
<td>脳血管異常症</td>
<td>5,198（72.0％）</td>
<td>5,200（71.8％）</td>
</tr>
<tr>
<td>糖尿病</td>
<td>2,445（33.9％）</td>
<td>2,458（33.9％）</td>
</tr>
<tr>
<td>BMI＞25kg/m²</td>
<td>2,644（36.6％）</td>
<td>2,604（35.9％）</td>
</tr>
<tr>
<td>吸煙</td>
<td>959（15.3％）</td>
<td>934（12.9％）</td>
</tr>
<tr>
<td>家族歴</td>
<td>1,981（27.4％）</td>
<td>1,982（27.4％）</td>
</tr>
<tr>
<td>平均SBP（SD）、mmHg</td>
<td>137.1（15.8）</td>
<td>137.2（15.6）</td>
</tr>
<tr>
<td>平均DBP（SD）、mmHg</td>
<td>77.7（10.4）</td>
<td>77.6（15.6）</td>
</tr>
<tr>
<td>平均TC（SD）、mg/dL</td>
<td>202.9（32.9）</td>
<td>203.6（32.5）</td>
</tr>
<tr>
<td>平均LDL（SD）、mg/dL</td>
<td>132.8（76.0）</td>
<td>131.0（75.9）</td>
</tr>
<tr>
<td>平均HDL（SD）、mg/dL</td>
<td>107.8（31.2）</td>
<td>107.7（32.0）</td>
</tr>
<tr>
<td>平均TG（SD）、mg/dL</td>
<td>132.8（76.0）</td>
<td>131.0（75.9）</td>
</tr>
<tr>
<td>平均FFP（SD）、mg/dL</td>
<td>107.8（31.2）</td>
<td>107.7（32.0）</td>
</tr>
<tr>
<td>平均HbA1C（SD）、％</td>
<td>6.1（1.0）</td>
<td>6.0（1.0）</td>
</tr>
<tr>
<td>平均BMI（SD）</td>
<td>24.2（3.5）</td>
<td>24.2（3.4）</td>
</tr>
</tbody>
</table>

BMIB: 脂満指数、DBP: 血圧基準値、FFP: 助血時血精鰐、HbA1c: グリコヘモグロビン、HDL: 高密度リボ蛋白、LDL: 低密度リボ蛋白、SBP: 攻撃期血圧、TC: 総コレステロール、TG: トリグリセリド。

例が発症した。すでに報告しているように、アスピリン投与群では非投与群より、脳卒中症発症前にTIAを経験した患者数が有意に少なかった(1)。両群の全脳卒中またはTIA累積発症率を図1Aに示す。5年の時点で、全脳卒中またはTIAの発症率に2群間で有意差は認められなかった(アスピリン投与群2,668例およびアスピリン非投与群2,299例、調整HR 0.927、95％CI：0.741～1.160、P=0.509)。図1Bは両群の全脳卒中累積率を示す。やはり5年の時点で両群の全脳卒中発症率に有意差は認められなかった(アスピリン投与群1,809例およびアスピリン非投与群1,828例、調整HR 1,011、95％CI：0.791～1.291、P=0.932)。図1Cには5年間の虚血性脳卒中累積発症率を示す。アスピリン投与群ではアスピリン非投与群より虚血性脳卒中の発生が少なくなかったが、有意差はなかった(アスピリン投与群1,199例およびアスピリン非投与群1,451%、調整HR 0.842、95％CI：0.631～1.123、P=0.240)。

ICHの詳細を表2に示す。脳出血症の発生は非投与群(15例)より投与群(28例)に多くなったが、くも膜下出血を含めると発症部位の分布に有意差はなかった(アスピリン投与群748例およびアスピリン非投与群511例、調整HR 1.463、95％CI：0.956～2.237、P=0.078、図1D)。

登録した全患者の脳卒中およびTIA発症に関する因子をCox回帰分析を用いて解析した(表3)。アスピリンは脳血管イベントに影響する因子ではなく、年齢70歳以上、喫煙、糖尿病が独立した危険因子であった。推定したパラメーターに従って、70歳以上2点、喫煙1点、糖尿患者1点としてこれらの合計点でリスクスコアを算出した。0点または1点を低リスク、2点以上を高リスクに分類した。アスピリン投与群と非投与群における脳血管イベントの5年累積発症率は、低リスク患者のみならず(アスピリン投与群1,154例およびアスピリン非投与群1,390例、HR 0.839、95％CI：0.529～1.330、P=0.4538)高リスク患者でも(アスピリン投与群2,722例およびアスピリン非投与群2,961例、HR 0.955、95％CI：0.739～1.234、P=0.7246、図2)、両群に有意差はなかった。

考察

アスピリンの脳卒中一次予防効果に関して、欧米諸国の臨床試験からは相反する結果が報告されている(14)。Antithrombotic Trials’ Collaboration (ATT)のメタ解析(15)では、アスピリンの脳卒中対照とのリスク比は0.95(95％CI：0.85～1.06)であり、脳卒中の一次予防に関してアスピリンによるリスクは低減効果はなかった。このメタ解析で、アスピリンは、虚血性脳卒中の発症リスクを減らしたが有意ではなく(対照と比較したアスピリンの率0.86、95％CI：0.74～1.00)、また、出血性脳卒中のリスクを増やしたが有意ではなかった(率比1.32、95％CI：1.00～1.75)。本研究の結果もこのメタ解析と同様であることから、脳卒中の危険因子を持つ高齢患者にこのメタ解析の結果を一般化する
ことに関問題なく、有意差はなかったが虚血性脳卒中の
低減効果は出血性脳卒中増加により相殺されることか
ら、アスピリンに脳卒中リスクの低減効果はないと結論
付ける。現在進行中の Study to Assess the Efficacy
and Safety of Enteric-Coated Acetylsalicylic Acid in
Patients at Moderate Risk of Cardiovascular Disease
(AARRIVE) 12, A Study of Cardiovascular Events in
Diabetes (ASCEND) 13, Aspirin in Reducing Events
in the Elderly (ASPREE) 14, International Standard

Randomised Controlled Trial Number (ISRCTN) 15 と
いった試験で、登録患者の大半が欧米人であるが、脳卒
中の一次予防におけるアスピリンの有効性と安全性の
民族差について、新たな情報を与えるだろう。

アスピリンは、重大な虚血性ならびに出血性イベント
の複合発症率を増加して臨床的効果が見込める患者に使
用しなければならない 16-19。日本の虚血性脳卒中の発症
率は米国より高く、西ヨーロッパと同程度であるが、出
血性脳卒中の発症率は米国および西ヨーロッパより高
い 6,20,21。したがって、脳卒中の一次予防にアスピリンを
使用した場合のリスク−利益プロファイルは、日本人と
欧米人では異なる可能性がある。実際に、一次予防に関
していれば、JPPP 集団の虚血性脳卒中発症率は ATT
より低い（年間 1.04％に対して 0.26％）、出血性脳卒
中発症率は ATT 集団より高い（年間 0.03％に対して
0.08％） 7。しかし、我々の JPPP の脳卒中サブ解析の結
果をみると、脳卒中一次予防の相対的純益は ATT が報
告したメタ解析の結果とほぼ同じであった 7。
ICHの5年累積発症率は、アスピリン投与群が0.748％、アスピリン非投与群が0.511％であった。JPPPPでは、ベースラインの平均収縮期血圧が137 mmHg、平均拡張期血圧が78 mmHgと血圧は全体として良好にコントロールされていたとはいえ、血圧の有病率は85％と高かった。久山町研究の結果3によれば、正常高血圧群（130～139/85～89 mmHg）の脳出血発症率は1,000人・年あたり1.2と報告されている。JPPPPの1群7,000人で計算すると5年間で42人と推定されることから、アスピリン投与群での38人、アスピリン非投与群での23人という値は同程度である。

また、久山町研究のデータには脳出血の発症率が高かった32年前のデータが含まれているため、比較的古いデータであること注意する必要がある。日本では血圧管理の進歩に伴って脳出血の発症率は徐々に低下している。しかしながら、日本の最近の脳卒中登録研究では、脳卒中に占める出血性脳卒中の割合は約25％であると報告されており、欧米諸国の割合に比べてまだ高いことがわかる30-32。前述の久山町研究では、正常高血圧者と1度高血圧患者では脳卒中の割合は23～30％であったと報告されている3。また、JPPPPでの脳出血の割合は、アスピリン投与群30％、アスピリン非投与群23％であった。以上のデータを総合すると、JPPPP集団のICH発症率は妥当であると考えられる。

虚血性脳卒中の発症率が比較的低かったのは、ベースラインのデータで示したとおり、脳卒中事件のコントロールが良好であったことによるものと考えられる11、18。しかし、脳卒中のある管理に関わらず、JPPPPではATTに比較して出血性脳卒中の発症が多かった7。ICHのなかで脳出血はアスピリン非投与群よりアスピリン投与群に多く認められたが、くも膜下出血および硬膜下血腫は2群とも同程度であった。脳出血の最強の危険因子は高血圧である19-25。Secondary Prevention of Small Subcortical Strokes (SPS3)試験26ではアスピリンの単独投与またはクロピドグレルとの併用投与が行われた症例で、収縮期血圧目標値を130～149 mmHgとするより、130 mmHg未満することにより出血性脳卒中の発症率が有意に低下することが示された。脳血管障害または心血管疾患に抗血栓薬を投与した患者の観察研究であるBleeding With Antithrombotic Therapy (BAT)試験27では、ICHの予防に最適な血圧カットオフ値は130/81 mmHgであったと報告されている。以上の結果に基づき、日本の高血圧治療ガイドライン2014では、抗血栓薬を投与している脳卒中患者の血圧目標値として130/80 mmHg未満を推奨している28。また、脳卒中治療ガイドライン2015でも抗血栓薬を投与中の患者について血圧130/80 mmHg未満を推奨している29。しかし、脳卒中の一次予防に抗血小板薬を投与している患者の血圧コントロールに関しては、確認の根拠がないため推奨が存在しない。脳卒中の一次予防のためにアスピリンを投与している患者でも、特にICHのリスクが高い日本人などのアジア人の脳出血リスクを低減するには、従来の血圧管理レベルよりも厳しい血圧コントロールが必要と考えられる。我々はJPPPPデータの血圧サブ解析を予定しており、虚血性および出血性イベントに対する血圧レベルの影響を詳細に解析する研究も組み込むことになっている。

Cox回帰分分析でJPPPP登録患者すべてのリスクコアを計算した結果、脳卒中イベントの危険因子は年齢＞70歳、喫煙、糖尿病であった。両群とも高血圧および脂質異常症の患者が多かったため、危険因子としての有意性が表に出なかった可能性がある。禁煙と糖尿病管理は、脳血管障害の危険因子を持つ高齢日本人にとって、脳血管イベントの余余リスクを低減するために改善可能な危険因子として重要であると考えられる。

本研究の限界として、本試験が二重盲検試験ではなくPROBE研究であったことがあげられる。しかしながら、以下にあげる理由により、本試験において選択バイアスの問題はなかったと考えている。スクリーニング時に選択基準を満たしかつ除外基準に該当しなかった適格な症例を各施設において連続症例として登録した。統計担当者は中央のコンピュータシステムで無作為割り付け順序を生成し、治療の割付けは上記のように本研究専用のウェブサイトで治験医師に伝えられた。先に詳しく報告したベースラインの特徴は、患者の統計学的特徴が疾患の危険因子も、2群間でバランスが取れていた。また,
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