Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes
A Randomized Controlled Trial

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Diabetes mellitus is a powerful risk factor for cardiovascular events. The Framingham Heart Study reported that diabetes was associated with odds ratios for coronary heart disease of 1.5 and 1.8 for men and women, respectively, and relative risks for stroke of 1.4 and 1.7 for men and women, respectively.1-3 Individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular events than those without diabetes.6

Several earlier investigations have shown that aspirin therapy is established as a secondary prevention strategy for cardiovascular events.7-9 Clinical guidelines have recommended that individuals with risk factors for coronary heart disease should take aspirin for primary prevention and for secondary prevention; in particular, those with diabetes were considered good candidates for aspirin except for those with contraindications.10-15 The American Diabetes Association recommends use of aspirin as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk, including those who are older than 40 years or who have additional risk factors, such as family history of coronary heart disease, hypertension, smoking, dyslipidemia, or albuminuria.16 Nonetheless, the clinical trial data for aspirin in primary prevention have not been conclusive.

Context Previous trials have investigated the effects of low-dose aspirin on primary prevention of cardiovascular events, but not in patients with type 2 diabetes.

Objective To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

Design, Setting, and Participants Multicenter, prospective, randomized, open-label, blinded, end-point trial conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2539 patients with type 2 diabetes without a history of atherosclerotic disease and who had a median follow-up of 4.37 years.

Interventions Patients were assigned to the low-dose aspirin group (81 or 100 mg per day) or the nonaspirin group.

Main Outcome Measures Primary end points were atherosclerotic events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary end points included each primary end point and combinations of primary end points as well as death from any cause.

Results A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the nonaspirin group (17.0 per 1000 person-years) (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, \( P = .16 \)). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; \( P = .0037 \)). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.44; log-rank test, \( P = .67 \)). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.

Conclusion In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

Trial Registration clinicaltrials.gov Identifier: NCT00110448

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tient are limited. Several large trials of aspirin for primary prevention have examined its effects in subgroups with diabetes; these subgroup analyses did not demonstrate a significant effect on reducing vascular events because they were underpowered.17-21 Thus, a primary prevention trial of aspirin for diabetic patients is needed.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial was undertaken to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

METHODS

The JPAD trial was a prospective, randomized, open-label, controlled trial with blinded end-point assessment. Patient enrollment started in December 2002 and was completed in May 2005; patients were followed up until April 2008. Patients were enrolled and followed up at 163 institutions throughout Japan. The institutional review board at each participating hospital approved this trial, and written informed consent was obtained from each patient.

Trial Protocol

Enrolled patients were randomly assigned to the aspirin group or the nonaspirin group. The randomization was performed as nonstratified randomization from a random number table. The study center prepared the sealed envelopes with random assignments and distributed them by mail to the physicians in charge at the study sites. Patients in the aspirin group were assigned to take 81 mg or 100 mg of aspirin once daily. Patients were followed up at each hospital visit or by telephone if necessary. Follow-up visits were scheduled every 2 weeks for patients seen in a clinic setting and every 4 weeks for patients seen in a hospital setting. Data for patients who were lost to follow-up were included at the day of last follow-up. Patients were allowed to use any concurrent treatment. Patients in the nonaspirin group were also allowed to use antiplatelet/thrombotic therapy, including aspirin, if needed and vice versa.

End Points

The primary end point was any atherosclerotic event, which was a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis) during the follow-up period. Key secondary end points were each primary end point and combinations of primary end points and death from any cause. Adverse events analyzed included gastrointestinal (GI) events and any hemorrhagic events other than hemorrhagic stroke. All potential primary end points, secondary end points, and adverse events were adjudicated by an independent committee on validation of data and events that was unaware of the group assignments.

Sample Size Calculation

For sample size calculation, we first estimated the incidences of cardiovascular and cerebrovascular events among Japanese diabetic patients. The incidence of cardiovascular death, myocardial infarction, and cerebrovascular events were 7.5, 7.5, and 8.0 events per 1000 Japanese diabetic patients per year, respectively, according to the Hi-sayama-cho study22 and Funagata study.23 The total incidence of the atherosclerotic events, including peripheral arterial disease, was suggested to be 3 times the aforementioned number by the Hypertension Optimal Treatment (HOT) study.24 Because the recent incidence of atherosclerotic events among Japanese individuals seemed relatively lower than that previously reported in Japan, we discounted 25% of the estimated 69 events that were expected to occur and estimated that 52 events per 1000 Japanese diabetic patients would occur annually.

Based on a 2-sided α level of .05, a power of 0.95, an enrollment period of 2 years, and a follow-up period of 3 years after the last enrollment, we estimated that 2450 patients would need to be enrolled to detect a 30% relative risk reduction for an occurrence of atherosclerotic disease by aspirin.19

Statistical Analyses

Efficacy comparisons were performed on the basis of time to the first event, according to the intention-to-treat principle, including all patients in the group to which they were randomized with patients lost to follow-up censored at the day of the last visit. Safety analyses were performed on data from all enrolled patients. Following the descriptive statistics, cumulative incidences of primary and secondary end points were estimated by the Kaplan-Meier method and differences between groups were assessed with the log-rank test. We used the Cox proportional hazards model to estimate hazard ratios (HRs) of aspirin use along with 95% confidence intervals (CIs). We used the χ² test or Fisher exact test to evaluate adverse events.

We also conducted subgroup analyses for predetermined subgroups: sex (men, women); age (younger than 65 years, 65 years or older); hypertensive
status (hypertensive, normotensive); smoking status (current or past smoker, nonsmoker); and lipid status (hyperlipidemia, normolipidemia). Using the Cox proportional hazard model, proportional hazard assumptions were assessed on the plots of log (time) vs log [-log(survival)] stratified by index variables. Patients with missing values for any selected variable were excluded from the analyses that used the variable.

All statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-Plus version 7.0 (Insightful Corp, Seattle, Washington). P values of less than .05 were considered statistically significant. An independent safety monitoring board monitored the safety and efficacy of the study after 2 years of follow-up for an interim assessment and at the end of the study.

RESULTS

Study Population

The study screened 2567 patients with type 2 diabetes mellitus without a history of atherosclerotic disease, including cardiovascular disease, stroke, and peripheral vascular disease, from December 2002 to May 2005 in 163 institutions (FIGURE 1). Six patients who withdrew their informed consent were excluded. Twenty-two patients met exclusion criteria. We randomly assigned 2539 patients as follows: 1262 patients in the aspirin group and 1277 patients in the nonaspirin group. Patients were followed up until April 2008. The median follow-up period was 4.37 years (95% CI, 4.35-4.39). A total of 193 patients were lost to follow-up, and data for those patients were censored at the day of last follow-up.

Baseline Clinical Characteristics

Baseline clinical characteristics, including treatments for diabetes, hypertension, and dyslipidemia and diabetic microvascular complications, were similar between the 2 groups (TABLE 1). Overall mean (SD) age was 65 (10) years; 55% of patients were men. Median duration of diabetes was 7.3 years in the aspirin group and 6.7 years in the nonaspirin group. Diabetes was well controlled in both groups: mean (SD) levels of glycated hemoglobin were 7.1% (1.4%) in the aspirin group and 7.0% (1.2%) in the nonaspirin group. The prevalence of hypertension and dyslipidemia was 58% and 53%, respectively. Blood pressure was well controlled in both groups: mean (SD) systolic pressure, 136 (15) mm Hg; mean (SD) diastolic pressure, 77 (9) mm Hg in the aspirin group and mean (SD) systolic pressure, 134 (15) mm Hg; mean (SD) diastolic pressure, 76 (9) mm Hg in the nonaspirin group.

By the end of the study, 123 patients (10%) in the aspirin group had stopped taking the study medication. Since aspirin therapy was allowed in the nonaspirin group, 6 patients (0.5%) had taken aspirin and 3 patients (0.2%) had taken other antiplatelet medication.

Efficacy Analysis

A total of 154 atherosclerotic events occurred (TABLE 2). The incidence of the primary end point of any atherosclerotic event, a composite of sudden death, death from cardiovascular or aortic causes, nonfatal acute myocardial infarction, unstable angina, exertional angina, nonfatal ischemic and hemorrhagic stroke, transient ischemic attack, and nonfatal aortic and peripheral vascular disease (atherosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis), was not significantly different in the aspirin group (68 events, 5.4%) than in the nonaspirin group (86 events, 6.7%) (HR, 0.80; 95% CI, 0.58-1.10; log-rank test, P = .16) (TABLE 2 and FIGURE 2).

The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; P = .0037). Other secondary coronary, cerebrovascular, and peripheral vascular disease end points are shown in Table 2; there were no significant differences between the aspirin group and the nonaspirin group in these end points. There were 2 deaths due to aortic dissection, both in the low-dose aspirin group, and 1 nonfatal aortic dissection in the nonaspirin group. A total of 13 hemorrhagic strokes occurred; the incidences in each group were similar (6 in the aspirin group and 7 in the
nonaspirin group). There was 1 fatal hemorrhagic stroke in the aspirin group and 4 in the nonaspirin group.

Death from causes other than cardiovascular events were as follows for the aspirin group and nonaspirin group, respectively: there were 15 and 19 deaths due to malignancy, 2 and 5 due to infection, 3 and 0 due to suicide, 2 and 0 due to traffic crashes, and 1 and 1 due to liver cirrhosis. Therefore, 23 patients in the aspirin group and 25 patients in the nonaspirin group died from causes other than cardiovascular events. Eight patients in the aspirin group and 3 patients in the nonaspirin group died from unknown causes. A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.4; log-rank test, \( P = .67 \)).

**Subgroup Analyses**

In the 1363 patients aged 65 years or older (719 in the aspirin group and 644 in the nonaspirin group), the incidence of atherosclerotic events was significantly lower in the aspirin group (45 events, 6.3%) than in the nonaspirin group (59 events, 9.2%) (HR, 0.68; 95% CI, 0.46-0.99; \( P = .047 \)). In the 1176 patients younger than age 65 years, there were 23 events in the aspirin group (4.3%), a difference that was not significant (HR, 1.0; 95% CI, 0.57-1.70; \( P = .98 \)). A formal test of interaction with age did not show a significant result (\( P = .27 \)). There were no significant differences between the aspirin group and nonaspirin group in other subgroup analyses, including men, women, hypertensive, normotensive, current or past smokers, nonsmokers, dyslipidemia, and normolipidemia (FIGURE 3).

**Safety**

The prespecified analysis of adverse events is shown in **TABLE 3**. The hemorrhagic events consisted of GI bleeding in 12 patients in the aspirin group and 4 in the nonaspirin group and retinal hemorrhage in 8 patients in the aspirin group and 3 in the nonaspirin group. In the aspirin group, 4 patients had serious adverse events that needed a transfusion; no patients in the non-
aspirin group required transfusion. Another 13 patients in the aspirin group had minor bleeding. There was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding, which occurred in 10 patients in the aspirin group and in 7 patients in the nonaspirin group.

**COMMENT**

Myocardial infarction and ischemic stroke are leading causes of mortality and morbidity in patients with type 2 diabetes. In the JPAD primary prevention trial of 2539 type 2 diabetic patients without documented cardiovascular disease, the incidence of the primary end point of total atherosclerotic events, consisting of coronary, cerebrovascular, and peripheral vascular events, was not significantly different in the group that received prophylactic aspirin (81 or 100 mg once daily) than in the nonaspirin group. With the exception of fatal coronary and cerebrovascular events, none of the prespecified secondary end points were reduced significantly in the low-dose aspirin group. The incidence of fatal coronary and cerebrovascular events, a prespecified secondary end point, was significantly reduced in the low-dose aspirin group (P = .0037). A benefit of low-dose aspirin on the primary end point also was suggested in the subgroup of patients aged 65 years or older, which had a significant 32% relative reduction in total atherosclerotic events (P = .047).

The cardiovascular mortality benefit was achieved with a small increase in cases of serious GI bleeding (4 patients in the aspirin group had bleeding that required transfusion), but no excess of fatal GI or cerebral hemorrhages.

The JPAD trial enrolled 2539 diabetic patients without documented coronary or cerebrovascular complications; the sample size was the largest among the previous primary prevention studies in respect to the number of diabetic patients enrolled. However, no difference was found in the effect of aspirin on the primary end point or most secondary end points.

The interpretation of these results is challenging because the overall event rates were low: 17 in 1000 Japanese diabetic patients. This is one-third of the event rate anticipated in our sample-size calculations, which were based on the Hisayama-cho22 and Funagata23 epidemiologic studies conducted in Japan in the 1990s. Current treatment of cardiovascular risk factors in patients with type 2 diabetes has improved since the 1990s and may have ac-

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**Table 2. Atherosclerotic Events**

<table>
<thead>
<tr>
<th></th>
<th>Aspirin Group</th>
<th>Nonaspirin Group</th>
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<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. per 1000 Person-Years</td>
</tr>
<tr>
<td>Primary end point: all atherosclerotic events</td>
<td>68 (5.4)</td>
<td>13.6</td>
</tr>
<tr>
<td>Coronary and cerebrovascular mortality</td>
<td>1 (0.08)</td>
<td>0.2</td>
</tr>
<tr>
<td>CHD events (fatal + nonfatal)</td>
<td>28 (2.2)</td>
<td>5.6</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>12 (1.0)</td>
<td>2.4</td>
</tr>
<tr>
<td>Stable angina</td>
<td>1 (0.08)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cerebrovascular disease (fatal + nonfatal)</td>
<td>28 (2.2)</td>
<td>5.6</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>1 (0.08)</td>
<td>0.2</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>22 (1.7)</td>
<td>4.4</td>
</tr>
<tr>
<td>Ischemic</td>
<td>5 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>5 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>5 (0.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>7 (0.6)</td>
<td>1.4</td>
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**Figure 2. Total Percentage of Atherosclerotic Events According to Treatment Group**

CI indicates confidence interval; HR, hazard ratio.
counted for the lower event rates: there is better control of glucose, blood pressure, and lipid levels in clinical practice. The baseline characteristics of patients in the JPAD trial were similar to those in previous studies except that body mass index was relatively lower in the JPAD trial than that in the previous studies, although similar to that in other studies of Japanese diabetics. A meta-analysis of primary prevention trials that included the British Doctors' Trial, the Physicians' Health Study, the Thrombosis Optimal Treatment (HOT) study, the Primary Prevention Project (PPP) trial, and the Women's Health Study showed that aspirin therapy significantly reduced the risk of total coronary heart disease, nonfatal myocardial infarction, and total cardiovascular events with a nonsignificant trend for decreased risk of stroke, cardiovascular mortality, and all-cause mortality. However, the evidence for aspirin in prevention of cardiovascular events in diabetic patients has been surprisingly scant. Previous studies investigating the effects of low-dose aspirin on primary prevention of cardiovascular events did not enroll solely diabetic patients but enrolled patients with hypertension in the HOT study; patients with 1 or more cardiovascular risk factors in the Thrombosis Optimal Treatment Trial and the PPP trial; and a healthy population in the British Doctors' Trial, the Physicians' Health Study, and the Women's Health Study.

Several large primary prevention trials have included subgroup analyses of patients with diabetes. The Physicians' Health Study of 22,071 healthy men randomized to receive 325 mg of aspirin every other day or placebo showed a significant reduction in myocardial infarction for the entire population, but there was no significant difference for the small number of individuals with diabetes in the 2 treatment groups (11/275 in the aspirin group and 26/258 in the placebo group). The Antithrombotic Trialists' Collaboration meta-analysis of 287 randomized trials reported effects of antiplatelet therapy (mainly aspirin) vs control in 135,000 patients and showed a nonsignificant 7% reduction in the odds for serious vascular events for the subgroup of 5126 patients with diabetes. Sacco et al described the effects of aspirin on atherosclerotic disease in patients with diabetes as a subgroup of the PPP trial, which investigated the effects of aspirin and vitamin E in a 2-by-2 factorial trial of 4995 patients with at least 1 known major cardiovascular risk factor. The original study was stopped on ethical grounds after a mean follow-up of 3.6 years because aspirin was associated with a lower risk of atherosclerotic disease in the overall group. The results of a subgroup analysis of 1031 diabetic patients did not

<table>
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<tr>
<th>Table 3. Adverse Effects</th>
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<tr>
<td></td>
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<tr>
<td>No.</td>
</tr>
<tr>
<td>Aspirin Group</td>
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<td>----------------</td>
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<tr>
<td>Bleeding, gastrointestinal&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Hemorrhagic gastric ulcer</td>
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<tr>
<td>Bleeding from esophageal varices</td>
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<td>Bleeding from colon diverticula</td>
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<tr>
<td>Gastrointestinal bleeding due to cancer</td>
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<tr>
<td>Hemorrhoid bleeding</td>
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<tr>
<td>Gastrointestinal bleeding (cause unknown)</td>
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<tr>
<td>Bleeding, other</td>
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<tr>
<td>Retinal bleeding</td>
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<tr>
<td>Bleeding after tooth extraction</td>
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<tr>
<td>Subcutaneous hemorrhage</td>
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<tr>
<td>Hematuria</td>
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<tr>
<td>Nose bleeding</td>
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<tr>
<td>Chronic subdural hematoma</td>
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<tr>
<td>Nonbleeding gastrointestinal event</td>
</tr>
<tr>
<td>Nonhemorrhagic gastritis</td>
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<tr>
<td>Nonhemorrhagic gastric ulcer</td>
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<tr>
<td>Nonhemorrhagic colonic ulcer</td>
</tr>
<tr>
<td>Only gastrointestinal symptom</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Asthma</td>
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<sup>a</sup> In the aspirin group, 4 cases of severe gastrointestinal bleeding required transfusion.

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reach statistical significance, possibly because of the early stopping of the trial and the subgroup size.\textsuperscript{20} In addition, medication adherence was poor in the PPP trial: 28.2% of subjects assigned to aspirin had stopped this therapy by the conclusion of the trial. In the JPAD study, only 10% of patients in the aspirin group stopped this therapy by the end of the mean 4.37 years of follow-up.

Because of the low event rate in JPAD, our study was underpowered for demonstrating that aspirin had a significant effect on reducing total atherosclerotic events. However, the observation in the JPAD trial of an effect of aspirin on the secondary outcome of fatal cardiovascular events was also seen in the PPP trial. Aspirin did not reduce cardiovascular mortality in the HOT study, and it did not reduce fatal stroke in the Women's Health Study. The reason for the discrepancy in the preventive effect of aspirin on fatal cardiovascular events is not clear at present. The total number of fatal events was small (ranging from 13 to 49) in the JPAD trial as well as the PPP trial and in the subgroup population with diabetes in the HOT study. A larger trial is needed to determine the efficacy of low-dose aspirin on mortality.

The JPAD trial composite primary endpoint also included hemorrhagic stroke. The finding that aspirin did not increase the risk of hemorrhagic stroke was consistent with findings from prior reports,\textsuperscript{21,24,30,31} although the population studied was patients with diabetes. The finding of no increase in hemorrhagic stroke in the JPAD trial is of particular clinical importance because hemorrhagic stroke is more common in Japanese populations than in the West.\textsuperscript{32,33} Moreover, there was no fatality due to hemorrhagic events except for hemorrhagic stroke; however, the hemorrhagic events that required surgical interventions or transfusion were observed in 4 patients in aspirin group.

The study design may be considered a limitation of the JPAD trial (prospective, randomized, open-label, controlled trial with blinded end-point assessment), as it did not have the advantages of a double-blind, randomizedized trial. The Japanese Pharmaceutical Affairs Law limits the use of placebo in physician-initiated studies because it is an unapproved medicine. However, the end-point classification was conducted by a blinded, independent committee on validation of data and events that was unaware of the group assignments.

Previous clinical studies indicate that a cardiovascular risk reduction is difficult to achieve by aggressively controlling plasma glucose levels in diabetic patients.\textsuperscript{34–37} These studies suggested that the contribution of lowering glucose levels to the reduction of macrovascular events appears to be minimal, at least in the first few years of treatment. Although improved glucose control can protect against the development of microvascular complications, the absence of a reduction in macrovascular events implicates an additive effect of nonglycemic risk factors that often accompany diabetes, such as hypertension, hyperlipidemia, and hypercoagulability. Additional medications such as angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, statins, and antiplatelet agents may be needed in patients with type 2 diabetes mellitus. The JPAD trial indicates that among these medications, aspirin is well tolerated for primary prevention and may provide an additional low-cost option.

In summary, in the JPAD trial, the first prospectively designed trial to evaluate low-dose aspirin in patients with type 2 diabetes without previous cardiovascular disease, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events. Despite a large sample size, the event rate in the study was lower than anticipated. Aspirin was well tolerated in these patients, as there was no increase in hemorrhagic strokes and a small increase in serious GI hemorrhagic events (4 patients required transfusion). These findings should be interpreted in context with the low incidence of atherosclerotic disease in Japan and the current management practice for cardiovascular risk factors and suggest the need to conduct additional studies of aspirin for primary prevention of cardiovascular disease in diabetic patients.

Published Online: November 9, 2008 (doi:10.1001/ jama.2008.623)

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Author Contributions: Dr Morimoto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Ogawa, Nakayama, Morimoto, Saito, Uemura.

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Critical revision of the manuscript for important intellectual content: Ogawa, Nakayama, Morimoto, Kanauchi, Jinnochi, Sugiyama, Saito.

Statistical analysis: Ogawa, Morimoto.

Obtained funding: Ogawa, Nakayama, Morimoto.

Administrative, technical, or material support: Ogawa, Nakayama, Morimoto, Uemura, Kanauchi, Doi, Jinnochi, Sugiyama, Saito.

Study supervision: Ogawa, Nakayama.

Financial Disclosures: Drs Ogawa, Nakayama, and Sugiyama reported receiving grant support for the past 5 years from the Ministry of Health, Labour and Welfare (Japan) and grant support and lecturer’s fees from Astellas, AstraZeneca, Banyu, Bayer Yakuhin, Boehringer Ingelheim, CatheX, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Get Bros, Guidant Japan, Japan Life-line, Kakou, Kissai, Kowa, Kyowa Hakko, Mitsubishi Tanabe, Mochida, Nihon Kohden, Nihon Schering, Novartis, Otsuka, Pfizer, Pharmacia, Sankyo, Sanofi-Aventis, Sanwa Kagaku Kenkyusho, Schering-Plough, Sionogi, Sumitomo, Taisho Toyama, Takeda, Mitsubishi Tanabe, Teijin, Toa Eyo, Tori, Toyama, Tyco Health-care Japan, Vitatron Japan, Zeria, Novo Nordisk, Higo Foundation for Promotion of Medical Education and Research, Japan Foundation for Applied Enzymology, Japan Heart Foundation, Japanese Society of Interventional Cardiology, Kimura Memorial Heart Foundation, Kumamoto Medical Society, Smoking Research Foundation, Takeda Foundation, and Takeda Science Foundation. Dr Jinnochi reported receiving grant support for the past 5 years from the Ministry of Health, Labour and Welfare (Japan) and grant support and lecturer’s fees from Astellas, AstraZeneca, Banyu, Bayer, Baxter, Boehringer Ingelheim, Boston Scientific, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Fukuda Denshi, Johnson & Johnson, Kirin, Kowa, Kyowa Hakko, Mochida, Nihon Kohden, Novartis, Novo, Otsuka, Pfizera, Sanofi-Aventis, Sanwa Kagaku Kenkyusho, Takeda, Mitsubishi Tanabe, Zeria, and Japan Heart Foundation. Dr Morimoto reported being a statistical consultant for the Research Institute for Production Development, a non-profit research foundation; receiving nonpurpose research grants from Bayer Yakuhin and Daiichi Sankyo; and receiving lecturer’s fees from Bayer Yakuhin, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Pfizer; and Pfizer for the past 5 years. Drs Uemura and Kanauchi reported receiving support from the Ministry of Health, Labour and Welfare (Japan) for the past 5 years. Dr Jinnochi reported receiving honoraria for lectures from Astellas, Banyu, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Sankyo, Sanofi-Aventis, Takeda, Sanwa Kagaku Kenkyusho, and Nuo Nordisk for the past 5 years. No other conflicts were reported.

Funding/Support: This study was supported by the Ministry of Health, Labour and Welfare of Japan.
Role of the Sponsor: The funding source had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.


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