Review

Aspirin for Primary Prevention of Atherosclerotic Disease in Japan

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Atherosclerotic disease is the most prevalent cause of death worldwide. The ratio of coronary heart disease/cerebrovascular disease differs between Japan and Western countries and the incidence of hemorrhagic stroke and gastrointestinal bleeding is higher in Japan. Thus, the threshold for aspirin administration for primary prevention has been controversial in Japan. Much anecdotal data from Western countries and from Japan has implied that the threshold for administering aspirin to those with risk factors for coronary heart disease is higher than that recommended in Western countries, and that the potential candidates for primary prevention in Japan seem to be diabetic patients. The Japanese primary Prevention of atherosclerosis with Aspirin for Diabetes (JPAD) trial involving 2,530 patients with type 2 diabetes started in December 2002. Compared to other primary prevention trials, this trial offered an acceptable sample size, a standard aspirin dosage, and gender balance. Because stroke is the most significant component of all atherosclerotic diseases in Japan, the impact of primary prevention with aspirin on stroke should be understood. Thus, the JPAD trial should generate reliable data on primary prevention with aspirin for diabetic patients that would also be relevant to other countries.

J Atheroscler Thromb, 2007; 14:159-166.

Key words: Coronary heart disease, Diabetes, Epidemiology, Randomized controlled trial

Introduction

Atherosclerotic disease includes coronary heart disease (CHD), and cerebrovascular and peripheral arterial diseases, and is associated with the highest rates of morbidity and mortality in developed countries¹. Many strategies for atherosclerotic disease, including medical approaches (use of HMG-CoA reductase inhibitors, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers and other antihypertensive and antidiabetic drugs), surgery, and percutaneous intervention have been widely applied over the past several decades. Despite progress in treatment modalities, CHD still accounts for the highest mortality rates in both high-income (17% of total death) and in other (12%) countries followed by cerebrovascular disease (10% of total death in high-income and other countries)¹. That is, atherosclerotic disease is the most prevalent global cause of death¹.

The epidemiology of atherosclerotic disease in the US and European countries differs from that in Japan. Levi et al. reported that the mortality from CHD in Japan was 36 per 100,000 age-standardized males compared with 121 in the US between 1995 and 1998². On the other hand, death from cerebrovascular disease accounted for 61 per 100,000 age-standardized males in Japan compared with 29 in the US². Although the incidence of CHD has recently increased and that of stroke has decreased in Japan³,⁴, this trend did not set off the ratio of CHD/cerebrovascular disease in Japan. Thus, cerebrovascular disease remains the major component of atherosclerotic disease in Japan compared with CHD in the US.

Morimoto et al. analyzed differences in the epidemiology of atherosclerotic disease in subsets of Japa-
Fig. 1. Estimated incidences of coronary heart disease in Japan and the United States.
Reprinted from American Journal of Medicine, Vol. 117 (7), Morimoto T et al., Application of U.S. guidelines in other countries: aspirin for the primary prevention of cardiovascular events in Japan. 459-468 (c) 2004 Excerpta Medica, Inc.
nese and US populations and predicted 5-year rates of CHD per 1,000 patients. The report considered “base case” patients in two age strata (40-64 and 65-79) to be those aged 50 or 70 without a history of dyslipidemia or smoking. For example, a 50-year-old male in the US without hypertension or diabetes would have a 3% risk of developing CHD in the next 5 years, but if this same person were Japanese, the risk would be 0.8% (Fig. 1). These data imply that the main target of treatment for atherosclerotic disease is CHD in the US. Therefore, the results of American clinical trials or practice guidelines are not necessarily applicable in Japan.

**Aspirin and Atherosclerotic Disease**

Aspirin has been used for the secondary prevention of atherosclerotic disease for over 5 decades. A meta-analysis has shown that the administration of a low dose of aspirin (≤325 mg/day) is associated with a 17% reduction in all cause mortality, and that the risk ratio of developing another atherosclerotic event was 0.7-0.8 with aspirin therapy. Because patients who have had CHD or cerebrovascular disease are at high risk for a second attack, the benefit of aspirin for secondary prevention has been established.

However, whether or not aspirin reduces the risk for atherosclerotic disease in “persons” (who may not be “patients”) without known atherosclerotic disease, namely, primary prevention, has remained controversial. After many randomized controlled trials to determine whether the use of aspirin is a viable method of preventing primary atherosclerotic disease in Western countries, a meta-analysis concluded that aspirin is significantly associated with a 32% reduction in nonfatal myocardial infarction. Although the results of this meta-analysis did not reach a level of statistical significance, patients taking aspirin had a 56% increase in hemorrhagic stroke. Because the burden of hemorrhagic stroke among patients with atherosclerotic disease is not large in the US or in Europe, aspirin was considered an effective therapeutic option for preventing atherosclerotic disease in these regions.

Based on these findings, the United States Preventive Service Task Force has developed guidelines for the use of aspirin to prevent CHD events for patients without a history of CHD. The Task Force used data from five randomized controlled trials to assess the likely effects of aspirin on CHD events among the general population without a history of this disease. The results indicated that aspirin should be considered for patients with a 5-year risk of CHD of 3% or more. Analyses within the guidelines suggested that aspirin in this population would prevent at least twice as many CHD events as the number of hemorrhagic complications it would cause.

Hemorrhagic complication is the sole disadvantage of aspirin therapy. A meta-analysis of secondary prevention trials found that the risk ratio of gastrointestinal bleeding is 2.5 with aspirin therapy and that the incidence of hemorrhagic stroke is increased by 56%, although the latter findings were not statistically significant.

A Japanese study of aspirin for secondary prevention showed a 21% reduction in cardiovascular events (CHD and ischemic stroke), but this value was not statistically significant. However, aspirin reduced reinfarction with an odds ratio of 0.27 for patients with a history of myocardial infarction. In terms of primary prevention, the effect of aspirin in persons without a history of atherosclerotic disease in Japan has not been investigated.

In addition, no data regarding the incidence of or mortality from major gastrointestinal bleeding with or without the use of aspirin are available in Japan. However, taking into account that the prevalence of Helicobacter pylori infection is higher in Japan, and that upper gastrointestinal bleeding in patients taking aspirin is associated with Helicobacter pylori infection, the incidence of major gastrointestinal bleeding could be higher in Japan. Moreover, the incidence of subarachnoid hemorrhage is much higher in Japan than in the US. The proportion of subarachnoid hemorrhage in all cases of stroke in Japan is 32%, but only 9% in the US, and a far higher dose of aspirin increased the risk of subarachnoid hemorrhage only in women. Therefore, the increased numbers of hemorrhagic complications of aspirin therapy would be more critical in Japan than in the US and Europe.

**Aspirin for Primary Prevention in Japan**

The Japanese Joint Research Committee for Cardiac Disease Guidelines advises physicians to “consider the use of aspirin for those with risk factors” without stating any specific risk threshold. As noted above, the incidence of CHD is lower in Japan than in the US, while that of cerebrovascular disease, especially hemorrhagic stroke, is higher. Although the incidence of CHD has recently been increasing and that of stroke is decreasing in Japan, the potential consequences of aspirin for primary prevention of atherosclerotic disease in Japan should be different from those in the US and Europe.

Like the United States Preventive Service Task Force, Morimoto et al. recently simulated the net
Table 1. Estimated benefit and harm of aspirin therapy for middle-aged patients at different levels of risk for coronary heart disease events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>US</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated 5-Year Risk for Coronary Heart Diseases Events at Baseline</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>No change</td>
<td>3 (1 to 4)</td>
</tr>
<tr>
<td>Coronary heart disease events avoided, n</td>
<td>No change</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic strokes avoided, n</td>
<td>1 (0 to 2)</td>
<td>1 (0 to 2)</td>
</tr>
<tr>
<td>Hemorrhagic strokes precipitated, n</td>
<td>3 (2 to 4)</td>
<td>3 (2 to 4)</td>
</tr>
<tr>
<td>Major gastrointestinal bleeding events precipitated, n</td>
<td>No change</td>
<td>3 (1 to 4)</td>
</tr>
<tr>
<td>Coronary heart disease events avoided, n</td>
<td>No change</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic strokes avoided, n</td>
<td>2 (0 to 5)</td>
<td>2 (0 to 5)</td>
</tr>
<tr>
<td>Hemorrhagic strokes precipitated, n</td>
<td>6 (4 to 8)</td>
<td>6 (4 to 8)</td>
</tr>
<tr>
<td>Major gastrointestinal bleeding events precipitated, n</td>
<td>No change</td>
<td>3 (1 to 4)</td>
</tr>
</tbody>
</table>


benefit of aspirin therapy by subtracting the predicted increase in the numbers of hemorrhagic stroke and major gastrointestinal bleeding events from the predicted avoided events of CHD among 1,000 Japanese individuals over a 5-year period. The analyses applied the odds ratios for the impact of aspirin on rates of CHD, hemorrhagic stroke, and major gastrointestinal bleeding used in the United States Preventive Service Task Force guidelines to the Japanese population. The applied odds ratios were 0.72 (95% confidence interval: 0.60-0.87) for CHD, 1.4 (0.9-2.0) for hemorrhagic stroke, and 1.7 (1.4-2.1) for major gastrointestinal bleeding. As a result, the analyses calculated a threshold 5-year risk of CHD for a hypothetical cohort of 1,000 Japanese that would be expected to yield the same 2:1 ratio of CHD events avoided to hemorrhagic events caused as was used in the United States Preventive Service Task Force guidelines to identify the recommended 3% threshold.

The analysis revealed that the expected harm from aspirin exceeded the benefit for most of the Japanese population. The United States Preventive Service Task Force guidelines showed that middle-aged men (aged 50-65 years) with a 5-year CHD risk of 3% would benefit from aspirin for primary prevention, with two coronary heart disease events prevented for every complication induced. In contrast, the analysis showed that a comparable population (men aged 40-64 years) has a 5-year CHD risk of only 0.8% and would be negatively, rather than positively, affected by aspirin. Only Japanese men with both hypertension and diabetes would benefit from aspirin as a primary preventive measure (Fig. 1). To identify a risk threshold that would be associated with a 2:1 ratio of prevented events to elicited complications, the 5-year CHD risk must be at least 6% for middle-aged (aged 40-64 years) normotensive Japanese patients. According to the results of these analyses, aspirin would be appropriate for middle-aged or elderly men with both hypertension and diabetes, or women with hypertension, diabetes, and such additional risk factors as dyslipidemia and smoking in Japan.

A major reason why the US guidelines for aspirin might be inappropriate for Japan is that the mortality from CHD is 4.3-fold higher in the US than Japanese population. Similarly, the baseline risk of CHD in the five studies used in the United States Preventive Service Task Force guidelines was 2.3-7.9-fold higher than the estimates for Japanese people. The analyses by the United States Preventive Service Task Force and Morimoto et al. fixed the precipitated incidence in hemorrhagic stroke and did not vary this risk with increasing CHD risk. In addition, the analyses assumed that aspirin has the same effects on risks of CHD and hemorrhagic complications on people in the US and in Japan. The popular dose of aspirin in Japan is 81-100 mg per day. Thus, if the effect of aspirin does in fact differ among populations, the results would also change. Because a meta-analysis previously showed that aspirin does not affect the risk of ischemic stroke, the high incidence of ischemic stroke among Japanese did not affect the key findings. Because aspirin ther-
apy is effective for secondary prevention of ischemic stroke in the US, the results could change if aspirin were found to be effective for the primary prevention of ischemic stroke in the Japanese population. Moreover, Morimoto et al. had to estimate the incidence of major gastrointestinal bleeding based on only one of 250 patients on aspirin from one secondary prevention trial.

From the patient’s perspective, the consequences of CHD, hemorrhagic stroke, and major gastrointestinal bleeding are not equivalent and preferences for and attitudes toward the various outcomes might influence the threshold at which a patient desires to use aspirin. Although the United States Preventive Service Task Force used this method, the CHD risk threshold was based on the incidence of fatal and nonfatal cases. To overcome these issues, a prospective randomized trial must be conducted to demonstrate primary prevention with aspirin in Japan.

### Aspirin for Diabetic Patients

These guidelines from the US or analyses from Japan implied that individuals with risk factors for CHD should take aspirin for primary prevention; in particular, those with diabetes except those with contraindications were considered good candidates. The Framingham Study reported that diabetes is a strong risk factor for CHD (odds ratios for men and women, 1.5 and 1.8, respectively) and stroke (relative risk for men and women, 1.4 and 1.7, respectively) within a Western population. This association was also evident in Japanese-American men, and validated in a Japanese population by the Hisayama Study.

### Table 2. Differences of characteristics between studies of primary prevention of aspirin

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMD</th>
<th>PHS</th>
<th>TPT</th>
<th>HOT</th>
<th>PPP</th>
<th>WHS</th>
<th>PPP subanalysis</th>
<th>JPAD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>United Kingdom</td>
<td>United States</td>
<td>United Kingdom</td>
<td>Worldwide</td>
<td>Italy</td>
<td>United States</td>
<td>Italy</td>
<td>Japan</td>
</tr>
<tr>
<td>Duration of therapy, y</td>
<td>5.8 (mean)</td>
<td>5.0 (mean)</td>
<td>6.8 (median)</td>
<td>3.8 (mean)</td>
<td>3.6 (mean)</td>
<td>10.1 (mean)</td>
<td>3.7 (median)</td>
<td>2.5 (median)</td>
</tr>
<tr>
<td>Included patients</td>
<td>Male physician</td>
<td>Male physician</td>
<td>Men at high risk for heart disease</td>
<td>Men and women with hypertension</td>
<td>Men and women with &gt;1 major risk factor for CHD</td>
<td>Healthy women</td>
<td>Men and women with diabetes</td>
<td>Men and women with diabetes</td>
</tr>
<tr>
<td>Patients (women), n</td>
<td>5139 (0)</td>
<td>22071 (0)</td>
<td>2540 (0)</td>
<td>18790 (8831)</td>
<td>4495 (2583)</td>
<td>39876 (39876)</td>
<td>1031 (534)</td>
<td>2530 (1145)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60y (47%); 60-69y (39%); 70-79y (17%)</td>
<td>Mean, 53y (range, 40-84y)</td>
<td>Mean 61.5y (range, 50-80y)</td>
<td>&lt;60y (29%); 60-69y (45%); 70-79y (24%)</td>
<td>Mean 61.5y (range, 50-80y)</td>
<td>Mean 61.5y (range, 50-80y)</td>
<td>Mean 61.5y (range, 50-80y)</td>
<td>Mean 61.5y (range, 50-80y)</td>
</tr>
<tr>
<td>Aspirin dosage</td>
<td>500 mg/d</td>
<td>325 mg every other day</td>
<td>75 mg/d</td>
<td>75 mg/d</td>
<td>100 mg/d</td>
<td>100 mg every other day</td>
<td>100 mg/d or 100 mg/d</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>No placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>No placebo</td>
<td>Placebo</td>
<td>No placebo</td>
<td>No placebo</td>
</tr>
<tr>
<td>Additional therapy</td>
<td>None</td>
<td>Beta-Carotene (50%)</td>
<td>None</td>
<td>Felodipine with or without ACE inhibitor or Beta-blocker</td>
<td>Vitamin E (50%)</td>
<td>Vitamin E (50%)</td>
<td>Vitamin E (50%)</td>
<td>None</td>
</tr>
<tr>
<td>CHD events/Aspirin patients</td>
<td>169/3429</td>
<td>163/11037</td>
<td>83/1268</td>
<td>82/9399</td>
<td>26/2226</td>
<td>198/19934</td>
<td>18/519</td>
<td>–</td>
</tr>
<tr>
<td>CHD events/Control patients</td>
<td>88/1710</td>
<td>266/11034</td>
<td>107/1272</td>
<td>127/9391</td>
<td>35/2226</td>
<td>193/19942</td>
<td>26/512</td>
<td>–</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.96</td>
<td>0.61</td>
<td>0.76</td>
<td>0.64</td>
<td>0.75</td>
<td>1.04</td>
<td>0.68</td>
<td>–</td>
</tr>
<tr>
<td>Annual risk for CHD events among control patients, %</td>
<td>0.89</td>
<td>0.48</td>
<td>1.24</td>
<td>0.36</td>
<td>0.43</td>
<td>0.096</td>
<td>1.4</td>
<td>–</td>
</tr>
</tbody>
</table>

*Data are at the point of June 2006

*p-value < 0.05

ACE = angiotensin-converting enzyme; BMD = British Male Doctors; CHD = coronary heart disease; HOT = Hypertension Optimal Treatment; JPAD = Japanese primary Prevention of atherosclerosis with Aspirin for Diabetes; PHS = Physicians’ Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; WHS = Women’s Health Study

However, diabetic patients were also at higher risk for hemorrhagic stroke according to the Honolulu Heart Program and Framingham Study. Although aspirin is established as a secondary prevention to treat diabetic patients with CHD, an actual randomized study is still required to attest the primary preventive effects of aspirin among diabetic patients.

Sacco et al. described the effects of aspirin on atherosclerotic disease in patients with diabetes as a subgroup of the Primary Prevention Project (PPP) trial. The original trial investigated the effects of aspirin and vitamin E in a 2-by-2 factorial trial of 4,495 patients with at least one known major cardiovascular risk factor. The original study was stopped after a mean follow-up of 3.6 years and showed that aspirin was associated with a lower risk of atherosclerotic disease. Because the original trial was stopped early, this subgroup analysis of 1,031 diabetic patients did not reach a level of statistical significance. Contrary to expectation, the effect of aspirin was lower in the diabetic than non-diabetic group in terms of total cardiovascular events, all-cause mortality, cardiovascular mortality, and stroke. Thus, a primary prevention trial of aspirin for diabetic patients is urgently needed.

We thus started the Japanese primary Prevention of atherosclerosis with Aspirin for Diabetes (JPAD) trial in December 2002. This study was a randomized, open label, active controlled, multi-center study in Japan. We examined patients with type 2 diabetes aged between 30 and 85 years, who had no known atherosclerotic diseases (CHD, any type of stroke, or peripheral vascular diseases) and who were not contraindicated for aspirin. The participants were randomly allocated to groups taking aspirin (81 or 100 mg per day) or not. The outcomes included cardiovascular death, including sudden death, CHD, cerebrovascular disease including both ischemic and hemorrhagic events, peripheral arterial disease, and hemorrhagic complications. This study was registered at ClinicalTrials.gov with identifier NCT00110448 (Principal Investigator: Hisao Ogawa). We finished enrolling 2,530 patients who had already been followed up for a median of 2.5 years in June 2006. Compared with other primary prevention trials, the JPAD trial offered an acceptable sample size, standard aspirin dosages, and gender balance (Table 2). Stroke has made up a significant proportion of all atherosclerotic diseases in Japan and therefore the impact of aspirin on stroke as primary prevention should be evaluated in Japan. The JPAD trial will undoubtedly provide reliable data regarding primary prevention using aspirin in diabetic patients in Japan, which would also be relevant to other countries.

Conclusions

Aspirin confers protective effects on patients with known atherosclerotic disease, i.e. secondary prevention, but its application to patients with risk factors for atherosclerotic disease but with no known events or to healthy individuals has been controversial. Recent trials in Western countries have confirmed that primary prevention with aspirin moderately reduces the incidence of CHD events. Because the incidence of hemorrhagic stroke and of gastrointestinal bleeding is higher in Japan, the threshold to prescribe aspirin for primary prevention should be carefully optimized. Although evidence that aspirin can play a primary preventive role has not been published in Japan, potential Japanese candidates for primary prevention seem to be diabetic patients based on current data from both Japan and other countries. To test this hypothesis, we started the JPAD trial of type 2 diabetic patients. The effect of aspirin on this population will be clarified in the near future.

Acknowledgments

This study was supported by a Japan Heart Foundation Grant for Research on Arteriosclerosis Update, and in part by grant H14-Seikatsu-025 from the Ministry of Health, Labor and Welfare of Japan.

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NCT00110448)