An Overview of the 4 Randomized Trials of Aspirin Therapy in the Primary Prevention of Vascular Disease

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Background: In the primary prevention of cardiovascular disease, in contrast to the recommendations of the American College of Chest Physicians and the American Heart Association, the US Food and Drug Administration recently stated that there was insufficient evidence to judge whether aspirin therapy decreases the risk of a first myocardial infarction.

Objective: To perform an overview of the 4 primary prevention trials of aspirin therapy to obtain the most reliable estimates of the effects of aspirin therapy on various vascular disease end points.

Methods and Results: These 4 trials included more than 51,000 subjects and 2284 important vascular events. Those assigned to aspirin therapy experienced significant reductions of 32% (95% confidence interval [CI], 21%-41%) for nonfatal myocardial infarction and 13% (95% CI, 5%-19%) for any important vascular event. There were possible small but nonsignificant increases in risks of vascular disease–related death (1%; 95% CI, −12% to 16%) and nonfatal stroke (8%; 95% CI, −12% to 33%). When strokes were subdivided by type, there was no significant effect of aspirin therapy on the risk of ischemic stroke, but, while based on small numbers, there was a 1.7-fold apparent increase (95% CI, 6%-269%) in the risk of hemorrhagic stroke, which did achieve statistical significance.

Conclusions: For the primary prevention of vascular disease, aspirin therapy confers significant beneficial effects on first myocardial infarction and, as a result, on any important vascular event; these effects are clinically important. Whether there is any reduction in vascular disease–related death or stroke associated with treatment remains unclear because of inadequate numbers of events in the primary prevention trials completed to date. More data on hemorrhagic stroke are also needed. In addition, randomized trial data, especially in women but also in men, are needed to help to formulate a rational public health policy for individuals at usual risk. Meanwhile, these data provide evidence for a significant benefit of aspirin therapy in the primary prevention of myocardial infarction.

Arch Intern Med. 2000;160:3123-3127

An overview of the 4 randomized trials of aspirin therapy in primary prevention to obtain the most reliable treatments effects on various vascular end points was performed. Those assigned to aspirin therapy experienced a significant reduction of 32% for nonfatal myocardial infarction (MI) and, as a result, a 13% significant reduction for any important vascular event. There were no significant effects on vascular disease–related death or nonfatal stroke, but the available data were compatible with either small benefits or small increased risks. When strokes were subdivided by type, there was no effect of aspirin therapy on ischemic stroke, but, while based on small numbers, there was an apparent increase in the risk of hemorrhagic stroke, which did achieve statistical significance.

Numerous randomized trials of secondary prevention have demonstrated that aspirin therapy confers conclusive net benefits on subsequent MI, stroke, and cardiovascular disease–related death among survivors of a wide range of occlusive events. Aspirin therapy also confers similar conclusive net benefits when administered during evolving MI.

The US Food and Drug Administration recently recognized aspirin’s wider benefits by expanding its professional labeling indications. In 1998, the US Food and Drug Administration extended aspirin’s indications to acute evolving MI and to wider categories of secondary prevention.1

In primary prevention, among apparently healthy individuals who have never had any signs or symptoms of an occlusive event, the US Food and Drug Administration stated there was insufficient evi-
MATERIALS AND METHODS

To perform the overview, we initially conducted a computerized search of the literature (for studies published from 1988 through 1998) to identify randomized trials of aspirin therapy in the primary prevention of cardiovascular disease. Our search was limited to published English-language articles. In addition, we searched the reference lists of published primary prevention trials of aspirin therapy3,7,8 and previously conducted overviews.9,10 The criteria for the inclusion of trials in the overview were as follows: (1) aspirin alone was used for the primary prevention of cardiovascular disease as opposed to a multifactorial intervention; (2) comparisons of outcomes were made between aspirin and placebo (or, in the British Doctors’ Trial, to open control); and (3) data on vascular disease–related deaths, MIs, and strokes were available. Outcomes examined in the overview were a combined end point of any important vascular event (vascular disease–related death [either cardiac or cerebrovascular disease], nonfatal MI, or nonfatal stroke) and vascular disease–related deaths, nonfatal MIs, and nonfatal strokes, separately. We also examined ischemic vs hemorrhagic subtypes of strokes.

We used the general variance-based method11 to combine information from the individual studies. For each individual study, the relative risk (RR) and attributable risk (AR) estimates and their associated variances were computed. The RR provides a measure of the strength of an association between an exposure and a disease. In contrast, the AR provides a measure of the excess incidence or, alternatively, the decreased incidence of disease attributable to the exposure. For the RR, each individual estimate was transformed by taking the natural logarithm before pooling. The combined estimates were obtained by weighting each individual estimate by the inverse of its variance. Approximate 95% confidence intervals (CIs) were formed based on the asymptotic normality of the combined estimates. For the RR, CIs were calculated by taking the exponential of the upper and lower limits for the CI around the natural logarithm of the RR.

Homogeneity was assessed using the χ² statistic, which sums up the weighted difference of each individual estimate from the pooled estimate.

dence to conclude that aspirin therapy reduces the risk of a first MI.1 This statement was likely to have been made because the only 2 reported trials2,3 were interpreted to show divergent results. The US Physicians’ Health Study2 of 22,071 men was terminated early by the external Data and Safety Monitoring Board primarily because of the emergence of a statistically extreme 44% reduction in risk of a first MI among aspirin takers (P<.001). The British Doctors’ Trial3 of 5,139 men showed no significant reduction, although an overview of the 2 showed a significant decrease of 32% in first MI (P<.001).4 Guidelines published by the American College of Chest Physicians5 and the American Heart Association6 concluded that aspirin therapy reduces the risk of a first MI but that the evidence on stroke and vascular disease–related deaths is inconclusive because of insufficient numbers of these events. In general, recommendations are complicated by the fact that the absolute benefits of any therapy are much lower among apparently healthy people than among those who have had a prior occlusive event or who are having an MI, while adverse effects tend to be the same in all categories of patients.

The recent publication of 2 additional trials of aspirin therapy in primary prevention—the Thrombosis Prevention Trial (N=3,499 men)7 and the Hypertension Optimal Treatment study (N=18,790 persons, of whom 47% were women)8—provides additional important contributions to the totality of evidence from the Physicians’ Health Study2 and the British Doctors’ Trial.3 The sample sizes of the newly conducted trials7,8 are approximately equal to that of the 2 previous trials and, therefore, double the amount of information on aspirin therapy in the primary prevention of cardiovascular disease.

RESULTS

The design features of the individual trials are shown in Table 1. The results of the Physicians’ Health Study of 22,071 and the British Doctors’ Trial of 5,139 were published in 1988. The results of the Thrombosis Prevention Trial of 5,085 and the Hypertension Optimal Treatment study of 18,790 (47% women) were published 10 years later (in 1998). The mean durations of treatment and follow-up were from 4 to 6 years. All studies randomized equal numbers of persons to aspirin therapy and placebo, except the British Doctors’ Trial, which used a 2:1 allocation ratio.

A total of 2284 vascular end points occurred among 51,085 participants. There was no evidence of heterogeneity among the trials. As shown in Table 2, the proportions of participants who experienced any important vascular event (combined end point of vascular disease–related death, nonfatal MI, or nonfatal stroke) were generally lower in the treated groups. There were also slightly lower proportions of vascular disease–related deaths in the treated groups for all trials except the Thrombosis Prevention Trial, in which there were more events in the treated group. For the combined end point of any important vascular event, there was a statistically significant 13% reduction in risk associated with aspirin therapy (RR, 0.87; 95% CI, 0.81-0.95). For vascular disease–related deaths, there were no apparent treatment effects, although the CIs were wide and included the most plausible small reductions in risk (RR, 1.01; 95% CI, 0.88-1.16).

As shown in Table 3, for nonfatal MI, there was a large statistically significant reduction associated with aspirin therapy (RR, 0.68; 95% CI, 0.59-0.79). This was also true for all MIs (RR, 0.72; 95% CI, 0.65-0.81) (data not shown).

For nonfatal stroke, there was no significant decrease and a possible but nonsignificant increase in risk associated with aspirin therapy (RR, 1.08; 95% CI, 0.88-1.33) (Table 3). This was also true for all stroke (RR, 1.07; 95% CI, 0.93-1.24) (data not shown). In the 3 trials2,3,7 that presented information on subtypes of stroke, there
were no significant differences in risk of ischemic stroke between the treatment groups (RR, 1.01; 95% CI, 0.79-1.30). Although based on small numbers of events, there was an apparent 69% increase in the risk of hemorrhagic stroke associated with aspirin therapy that did achieve statistical significance (RR, 1.69; 95% CI, 1.06-2.69) (Table 4).

**COMMENT**

This overview of the 4 primary prevention trials provides strong support to the initial findings from the Physicians' Health Study\(^2\) that aspirin therapy significantly reduces the risk of a first MI in apparently healthy individuals. Thus, based on small numbers of events, which results in wide CIs, there is an approximate significant 1.7-fold increase in the risk of hemorrhagic stroke in this overview of 4 primary prevention trials. There was, in addition, a nonsignificant 9% reduction in the risk of nonvascular disease–related deaths (data not shown) associated with aspirin therapy that should be clarified as more data become available from ongoing and planned trials.

Aspirin therapy confers a clear benefit of preventing a first MI in apparently healthy and high-risk individuals. The magnitude of the risk reductions appears to be similar (about 30%) in primary and secondary prevention trials. In contrast, as would be expected, the absolute reduction in the risk of an MI associated with aspirin use is greater in high-risk than in low-risk individuals. For example, in a recent overview\(^6\) in which most trials included were conducted in patients with ischemic heart or cerebrovascular disease, the AR reduction was 137 MIs per 10000 persons and the number needed to treat to prevent 1 event was 73. In contrast,
the AR reduction in our overview of primary prevention trials was 67 MIs per 10000 persons and the number needed to treat to prevent 1 event was 150.

For hemorrhagic stroke, recent overviews of secondary and primary prevention trials are compatible with the possibility that aspirin therapy is associated with an increased risk. The summary RR in primarily secondary prevention trials conducted by He et al of 1.84 was similar to our RR of 1.69 in the present overview of primary prevention trials. However, the CIs surrounding these point estimates are wide and more data are needed. Estimates of the absolute increase in risk of hemorrhagic stroke associated with aspirin use have remained fairly consistent over time in overviews of secondary and primary prevention. The excess risk was originally reported at 1 to 2 per 10000 persons by the Antiplatelet Trialists' Collaboration, at 12 per 10000 in the overview by He et al, and at 11 per 10000 in the present overview. Using our AR of 11 per 10000 persons, the number needed to treat to cause 1 hemorrhagic stroke is 909.

Thus, in summary, in data from numerous trials of secondary prevention, treatment with aspirin of 10000 persons would prevent 137 MIs and would cause 12 hemorrhagic strokes. Based on the available data from the 4 trials of primary prevention, treatment of 10000 persons would prevent 67 MIs and would cause approximately the same number (11 per 10000 persons) of hemorrhagic strokes as observed in secondary prevention trials. These comparisons reinforce the observation that the absolute benefits of aspirin therapy are lower among apparently healthy individuals than among those who have had a prior occlusive event or those who are having an MI, while the frequency of adverse effects tends to be the same.

Additional data are needed to accurately determine the benefit-risk ratio of aspirin therapy in apparently healthy individuals. Critical questions include the impact of aspirin therapy on vascular disease–related death and on overall, ischemic, and hemorrhagic stroke. Furthermore, most of the primary prevention trial data accumulated thus far are in men. Randomized data in

Table 3. Nonfatal Myocardial Infarctions (MIs) and Nonfatal Strokes in 4 Randomized Trials of Aspirin Therapy in the Primary Prevention of Vascular Disease

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Allocated Active Treatment</th>
<th>Allocated Control Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonfatal MI</td>
<td>Nonfatal Stroke</td>
</tr>
<tr>
<td>Physicians' Health Study</td>
<td>129</td>
<td>110</td>
</tr>
<tr>
<td>British Doctors' Trial</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td>Thrombosis Prevention Trial</td>
<td>94</td>
<td>33</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Total</td>
<td>303</td>
<td>204</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.68</td>
<td>1.08</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.59-0.79</td>
<td>0.88-1.33</td>
</tr>
</tbody>
</table>

* A 2:1 randomization of treatment to control was used.
† The relative risk estimates for all MIs (relative risk, 0.64; 95% confidence interval, 0.49-0.85) and for all strokes (relative risk, 0.98; 95% confidence interval, 0.79-1.24) were similar to those found in the overview. Ellipses indicate data not available.

Table 4. Subcategories (Ischemic vs Hemorrhagic) of All (Fatal Plus Nonfatal) Stroke in 4 Randomized Trials of Aspirin Therapy in the Primary Prevention of Vascular Disease

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Allocated Active Treatment</th>
<th>Allocated Control Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ischemic Stroke</td>
<td>Hemorrhagic Stroke</td>
</tr>
<tr>
<td>Physicians' Health Study</td>
<td>91</td>
<td>23</td>
</tr>
<tr>
<td>British Doctors' Trial</td>
<td>21</td>
<td>13</td>
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<tr>
<td>Thrombosis Prevention Trial</td>
<td>21</td>
<td>12†</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Total</td>
<td>133</td>
<td>48</td>
</tr>
<tr>
<td>Statistical analysis</td>
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<td>.</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.01</td>
<td>1.69</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.79-1.30</td>
<td>1.06-2.69</td>
</tr>
</tbody>
</table>

* A 2:1 randomization of treatment to control was used.
† Includes subarachnoid hemorrhages.
‡ Ellipses indicate data not available.
women are also needed since the benefit-risk ratio of aspirin therapy in the primary prevention of cardiovascular disease may vary by sex. In this regard, the ongoing Women's Health Study\(^2\) of aspirin therapy among 40,000 female health professionals in conjunction with the already existing data from the Hypertension Optimal Treatment study will provide more reliable evidence of the benefits and risks of aspirin use in healthy women.

For the primary prevention of vascular disease, aspirin therapy confers significant beneficial effects on first MI and on any important vascular event; these effects are clinically important. Whether there is any reduction in vascular disease–related death, overall stroke, or ischemic stroke associated with aspirin therapy remains unclear because of inadequate numbers of events in the primary prevention trials completed to date. More data on hemorrhagic stroke are also needed. In addition, randomized trial data, especially in women but also in men, are needed to formulate a rational public health policy for individuals at usual risk. In the meanwhile, these data provide evidence for a significant benefit of aspirin therapy in the primary prevention of MI.

The data from this overview also reaffirm that the decision to use low-dose aspirin therapy remains an individual clinical judgment between physicians and their patients. Whether to recommend aspirin therapy for an individual patient involves assessing the patient's cardiovascular risk profile and then weighing the clear benefit of reducing the risk of a first MI against the adverse effects of long-term administration. When the physician decides that the benefits outweigh the risks, aspirin therapy should be used as an adjunct—not an alternative—to managing other cardiovascular risk factors.

Accepted for publication February 1, 2000.

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REFERENCES