An Update on Aspirin in the Primary Prevention of Cardiovascular Disease

Rachel S. Eidelman, MD; Patricia R. Hebert, PhD; Steven M. Weisman, PhD; Charles H. Hennekens, MD, DrPH

Background: In 1988, the aspirin component of the Physicians’ Health Study, a randomized, double-blind, placebo-controlled trial of 22071 apparently healthy men was terminated early, due principally to a statistically extreme (P < .00001) 44% reduction in the risk of a first myocardial infarction (MI). The Cardio-Renal Drugs Advisory Committee recommended that the US Food and Drug Administration approve professional labeling of aspirin to prevent first MI. The agency did not act on this recommendation because the only other trial, the British Doctors’ Trial of 5139 men, showed no significant benefits. Since that time, 3 additional randomized trials (which included men and women) of aspirin in the primary prevention of MI have been published.

Methods: A computerized search of the English literature from 1988 to the present revealed 5 published trials: the Physicians’ Health Study (22071 participants), the British Doctors’ Trial (5139), the Thrombosis Prevention Trial (5085), the Hypertension Optimal Treatment Study (18790), and the Primary Prevention Project (4495).

Results: Among the 55580 randomized participants (11466 women), aspirin was associated with a statistically significant 32% reduction in the risk of a first MI and a significant 15% reduction in the risk of all important vascular events, but had no significant effects on non-fatal stroke or vascular death.

Conclusions: The current totality of evidence provides strong support for the initial finding from the Physicians’ Health Study that aspirin reduces the risk of a first MI. For apparently healthy individuals whose 10-year risk of a first coronary event is 10% or greater, according to the US Preventive Services Task Force and the American Heart Association, the benefits of long-term aspirin therapy are likely to outweigh any risks.

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From 1988 to 1998 we conducted a computerized search of the English literature and identified 4 published randomized trials of aspirin in the primary prevention of CVD. In our previous meta-analysis of these trials, aspirin therapy significantly reduced the risk of a first MI by 32% and the risk of any important vascular event (nonfatal MI, nonfatal stroke, or vascular death) by 13%. From 1998 to the present, a subsequent meta-analysis of these trials, aspirin therapy significantly reduced the risk of any important vascular event among aspirin users. In the HOT trial, 18,790 participants (9,907 men and 8,883 women) aged between 50 and 80 years who had diastolic blood pressure measurements between 100 and 115 mm Hg were randomized in a 2 × 2 factorial design to 75 mg/d of controlled-release aspirin (supplied by Bayer); 5 mg/d of felodipine with variable escalating doses; both active agents; or placebo for 4 years. This trial demonstrated a significant 36% decrease in the risk of a first MI as well as a significant 15% reduction in the risk of any important vascular event among aspirin users.7

### Table 1. Features of the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Subjects randomized, No.</td>
<td>22,071</td>
<td>5,139</td>
<td>5,085</td>
<td>18,790</td>
<td>4,495</td>
</tr>
<tr>
<td>Patient population</td>
<td>Apparently healthy male physicians</td>
<td>6 (mean)</td>
<td>6 (mean)</td>
<td>4 (mean)</td>
<td>3.6 (mean)</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>40–84</td>
<td>50–78</td>
<td>45–69</td>
<td>50–80</td>
<td>50–80+</td>
</tr>
<tr>
<td>Age range, y</td>
<td>Male physicians</td>
<td>50–78</td>
<td>0</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>57.7</td>
</tr>
<tr>
<td>Aspirin dosage</td>
<td>325 mg every other day</td>
<td>500 mg/d</td>
<td>75 mg/d (controlled release)</td>
<td>75 mg/d</td>
<td>100 mg/d</td>
</tr>
</tbody>
</table>

### METHODS

#### OBJECTIVE

From 1988 to 1998 we conducted a computerized search of the English literature and identified 4 published randomized trials of aspirin in the primary prevention of CVD. In our previous meta-analysis of these trials, aspirin therapy significantly reduced the risk of a first MI by 32% and the risk of any important vascular event (nonfatal MI, nonfatal stroke, or vascular death) by 13%. From 1998 to the present, a subsequent review of the English literature revealed 1 additional primary prevention trial of aspirin as well as new guidelines on the use of aspirin in the primary prevention of CVD.

The fifth and most recently published trial of aspirin in the primary prevention of MI is the Primary Prevention Project. In this trial, 44,985 apparently healthy men (1912) and women (2583) aged from 50 to more than 80 years who had 1 or more major risk factors for CVD were randomized in a 2 × 2 factorial design to take 100 mg/d of enteric-coated aspirin (supplied by Bayer AG); 300 mg/d of vitamin E; both active agents; or open control. The trial was terminated early principally because of a significant 23% reduction in the risk of all cardiovascular events and of a 44% reduction in the risk of cardiovascular death among aspirin users, in the context of the beneficial effects of aspirin in the previously reported individual trials and their meta-analysis. There was also a possible but nonsignificant 31% reduction in the risk of MI and a 33% reduction in the risk of stroke.

Recently, the US Preventive Services Task Force and the American Heart Association issued new guidelines for aspirin in the primary prevention of MI in apparently healthy men and women. In this article, we update our meta-analysis and address the recently reported guidelines.

### DATA SOURCES AND STUDY SELECTION

To perform the meta-analysis, we used the published data from the PHS, the British Doctors’ Trial, the Thrombosis Prevention Study, the HOT study and the Primary Prevention Project (Table 1). The outcomes examined were the same as those used for the meta-analysis of secondary prevention, namely, a combined end point of any important vascular event (nonfatal MI, nonfatal stroke, or vascular death), and each of these individual components separately.

The criteria for inclusion of trials were as follows: (1) aspirin alone was used for the primary prevention of CVD, as opposed to combined interventions; (2) comparisons of outcomes were made between aspirin groups and either placebo or open control groups; and (3) data were available on MI, stroke, and vascular deaths.

### DATA EXTRACTION

We performed stratified analyses by trial to avoid direct comparisons between individuals within trials. We calculated the difference between the observed (O) and the expected (E) number of events, and its variance, from standard 2 × 2 tables of outcome by treatment. Difference and variance (V) were then summed over trials to give the grand total for O–E events and its V. We then based significance tests on comparisons of z scores, with $z = (O − E)/\sqrt{V}$, assuming the standard normal distribution and $P$ denoting the 2-sided significance level. The typical odds ratio for these trials was calculated by the 1-step method from $b = (O − E)/\sqrt{V}$, either as $exp(b)$ or, for rare events, as $(2 + b)/(2 − b)$. For odds ratios between 0.5 and 2, these 2 methods gave almost identical answers.

The British Doctors’ Trial used a 2:1 randomization ratio, so we multiplied the control group in this trial by 2 when calculating “adjusted” control totals. When comparing the percentages affected in the treatment and in the adjusted control groups, we calculated the standard error of the difference (D) between these percentages as $D/\sqrt{O}$. ©2003 American Medical Association. All rights reserved.
A total of 2402 CVD end points occurred among 55580 randomized participants (11466 women). There was no significant evidence of heterogeneity among the trials.

Table 2 shows the number of participants who experienced nonfatal MI and nonfatal stroke. For nonfatal MI, there was a statistically significant risk reduction of 32% associated with aspirin therapy (relative risk [RR], 0.68; 95% confidence interval [CI], 0.59-0.79). For nonfatal stroke, there was no significant effect but the CIs included the plausible decrease seen in the trials of secondary prevention,12 as well as a small-to-moderate increase (RR, 1.06; 95% CI, 0.87-1.29).

With respect to stroke subtypes, Table 3 shows a small, nonsignificant 3% reduction in ischemic stroke, but the CIs were wide (RR, 0.97; 95% CI, 0.77-1.22). For hemorrhagic stroke, although based on small numbers of events, there was a 56% increase, which was of borderline statistical significance (RR, 1.56; 95% CI, 0.99-2.46).

Table 4 shows that the proportion of participants who experienced any important vascular event (combined end point of vascular death, nonfatal MI, or nonfatal stroke) was generally lower in the aspirin groups. In the meta-analysis, there was a statistically significant 15% reduction in the risk of any important vascular event associated with aspirin therapy (RR, 0.85; 95% CI, 0.79-0.93). For vascular deaths, there was no significant reduction in risk although the CIs were wide and included the plausible decrease seen in the trials of secondary prevention,12 as well as a small increase (RR, 0.98; 95% CI, 0.85-1.12).

The current totality of evidence provides strong support for the initial findings from the PHS1,2 that aspirin significantly reduces the risk of a first MI by 32%
Table 4. Any Important Vascular Event and Vascular Death in the 5 Randomized Trials
of Aspirin in the Primary Prevention of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aspirin</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>PHS</td>
<td>307</td>
<td>81</td>
</tr>
<tr>
<td>BDT</td>
<td>289</td>
<td>148</td>
</tr>
<tr>
<td>TPT</td>
<td>228</td>
<td>101</td>
</tr>
<tr>
<td>HOT</td>
<td>315</td>
<td>133</td>
</tr>
<tr>
<td>PPP</td>
<td>47</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>1186</td>
<td>480</td>
</tr>
</tbody>
</table>

Statistical analysis

| Relative risk | 0.85 | 0.98 |
| 95% Confidence interval | 0.79-0.93 | 0.85-1.12 |

Abbreviations: BDT, British Doctors’ Trial; HOT, Hypertension Optimal Treatment study; PHS, Physicians’ Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial.

and any important vascular event by 15%, but there are still insufficient numbers of strokes or vascular deaths to yield conclusive results. The magnitude of reduction in risk of a first MI is similar to that published in the secondary prevention trials, nonetheless, since the absolute risks are much lower in primary than in secondary prevention, the absolute benefits are similarly lower.

For hemorrhagic stroke, overviews of secondary and primary prevention trials suggest an increased risk of about 1 to 2 per 1000 patients. These comparisons reinforce the observation that in primary and secondary prevention trials, serious adverse effects, principally hemorrhagic stroke, tend to be about the same.

Of the 5 primary prevention trials of aspirin completed to date, HOT randomized 8883 women and the Primary Prevention Project, for a total of 11 466. In HOT, subgroup analyses were presented for women and there was a possible but nonsignificant 19% reduction in risk of a first MI. In the Primary Prevention Project, the authors reported that the magnitude of benefit in women and men equaled the overall 31% reduction in risk of a first MI. Thus, the overall point estimate of the reduction in risk of a first MI for women who use aspirin therapy is about 22%, but the numbers of strokes and vascular deaths remain insufficient for analysis. In this regard, if a daily dose of 50 mg has clinical relevance, the ongoing Women’s Health Study should provide important relevant information on the effect of aspirin on stroke and its subtypes, as well as vascular death. In the meta-analysis of secondary prevention trials, daily doses of 75 mg to more than 1500 mg demonstrated a significant 25% (±3% SE) reduction in important vascular events. In the meta-analysis of the 3 secondary prevention trials of less than 75 mg of aspirin daily, the corresponding estimate was 13% (±8% SE).

Despite conclusive data from the trials of secondary prevention and professional labeling by the Food and Drug Administration, there is underutilization and mismedication with aspirin. As regards underutilization, in a recent survey, fewer than 50% of eligible patients in secondary prevention were prescribed aspirin. With respect to mismedication, 21% of the patients prescribed aspirin were actually taking acetaminophen (11%) or nonsteroidal anti-inflammatory drugs (10%). The absolute benefit of aspirin is greater to the individual patient in secondary prevention and greater to the health of the general public in primary prevention. Thus, the more widespread and appropriate use of aspirin would prevent more than 25,000 premature CVD events per year in secondary prevention but more than 150,000 in primary prevention.

With respect to aspirin in the primary prevention of CVD, considerations for use include the 10-year risk of the individual, the side effects of the long-term administration of aspirin, and the clear reduction in risk of a first MI. The US Preventive Services Task Force and the American Heart Association recommend aspirin for men and women whose 10-year risk of a first coronary event is 10% or greater. These recommendations are virtually identical to the results of a previous meta-analysis of risks. This 10-year risk of 10% or greater is also the level at which the recently published National Cholesterol Education Program guidelines recommend initiation of statin treatment for apparently healthy individuals with low-density lipoprotein cholesterol levels higher than 130 mg/dL (3.36 mmol/L). Furthermore, the different mechanisms of action of aspirin (primarily on thrombosis) and statins (primarily on atherosclerosis) suggested that their benefits were additive, and recent data have demonstrated this to be the case. An unanswered question, however, is the identification of the particular risk factors for the subgroups of apparently healthy men and women who are at such increased risk of a first MI that the benefits of aspirin clearly outweigh the risks.

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REFERENCES