Meta-Analysis of Data from the Six Primary Prevention Trials of Cardiovascular Events Using Aspirin

Alfred A. Bartolucci, PhD*, and George Howard, DrPH

Until recently, 5 major studies have formed the basis for the use of aspirin (acetylsalicylic acid) in primary prevention of cardiovascular (CV) events. Despite these data, the role of aspirin in primary prevention has not been established firmly. Six randomized trials have evaluated the benefits of aspirin for the primary prevention of CV events: the British Doctors’ Trial, the Physicians’ Health Study, the Thrombosis Prevention Trial, the Hypertension Optimal Treatment study, the Primary Prevention Project, and the Women’s Health Study. The combined sample consists of 47,293 subjects on aspirin and 45,580 not on aspirin or placebo. A meta-analysis of these 6 trials assessed 6 CV end points: total coronary heart disease (CHD), nonfatal myocardial infarction (MI), total CV events, stroke, CV mortality, and all-cause mortality. No covariate adjustment was performed and appropriate tests for treatment effect, heterogeneity, and study size bias were applied. Using odds ratios and confidence intervals, the meta-analysis suggested superiority of aspirin for total CHD, nonfatal MI, and total CV events (p ≤0.001 in each case), with a nonsignificant trend (0.07 < p < 0.34) for decreased risk of stroke, CV mortality, and all-cause mortality. There was no evidence of statistical bias (p >0.05). Given the study size and cohort, aspirin decreased the risk of CV events in this large patient sample. In conclusion, primary prevention with aspirin decreased the risk of total CHD, nonfatal MI, and total CV events, but there were no significant differences in the incidences of stroke or CV mortality. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:746–750)

Aspirin is an antiplatelet agent that inhibits platelet thromboxane A₂ production, and therefore, thrombus formation. Aspirin has been shown to be effective for the primary and secondary prevention of atherothrombotic disease. With the recent completion of the Women’s Health Study (WHS), there are 6 trials that have assessed the benefits of aspirin in the primary prevention of cardiovascular (CV) events: British Doctors’ Trial (BDT), Physicians’ Health Study (PHS), Thrombosis Prevention Trial (TPT), Hypertension Optimal Treatment (HOT) study, Primary Prevention Project (PPP), and the WHS. Meta-analyses of the first 5 trials demonstrated a positive outcome for total coronary heart disease (CHD) events and nonfatal myocardial infarction (MI), but not for CV death, total stroke, or all-cause mortality. The aim of the present analysis is to add data from the WHS to enlarge the sample and thus the power and precision. The WHS was the first large primary prevention trial to show that aspirin decreases the risk of stroke without affecting the risk of MI or death from CV causes. By adding the WHS data to the analysis, it is increasingly possible to detect moderate, but potentially meaningful, differences that individual trials cannot detect.

It is important to review the size and contribution of each of the 6 trials to the overall goal of evaluating aspirin as an effective primary prevention therapy. The main results are listed in Table 1.

A brief overview of the main features and results of each study are presented in the following.

The BDT was a 6-year randomized trial conducted among apparently healthy male doctors to determine whether 500 mg/day of aspirin decreased the incidence of stroke, MI, or other vascular conditions. Although total mortality was 10% lower in the aspirin group, this difference was not statistically significant and was mainly due to outcomes other than MI or stroke.

The PHS was a randomized, double-blind, placebo-controlled trial of 2 × 2 factorial designed to determine whether low-dose aspirin (325 mg every other day) decreased CV mortality, and whether β-carotene decreased the incidence of cancer, among apparently healthy male physicians. There was a 44% decrease in the risk of MI (RR 0.56, 95% confidence interval 0.45 to 0.70, p <0.0001); however, this decreased risk of MI with aspirin was apparent only in those ≥50 years of age (p = 0.02). Although there was a significant decrease in the risk of MI, the evidence for stroke and total CV deaths was inconclusive due to the small number of these events. An overview analysis of the BDT and PHS showed a significant 33% decrease in the risk of nonfatal MI with aspirin (p <0.0002). Only the main effects of aspirin on the CV end points are included in this meta-analysis.

The Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama. Manuscript received January 26, 2006; revised manuscript received and accepted April 6, 2006.

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* Corresponding author: Tel: 205-934-4905; fax: 205-975-2540.
E-mail address: albartol@uab.edu (A.A. Bartolucci).
The TPT had a factorial design involving aspirin and placebo, with or without warfarin, with the goal of decreasing the risk of CHD in men at high risk of, but without a history of, ischemic heart disease. Aspirin was associated with a significant decrease in the incidence of nonfatal stroke, CHD, nonfatal CHD, and CV events compared with placebo.

In the HOT study, patients with hypertension were randomly assigned aspirin (75 mg/day) or placebo. The results showed a significant decrease in nonfatal and fatal MI and death due to CHD. Specifically, aspirin decreased the incidence of major CV events by 15% (p = 0.03) and total MI by 36% (p = 0.002).

The PPP was a 2 × 2 factorial study of aspirin versus no aspirin, with and without vitamin E (vitamin E data were not considered in this meta-analysis). Aspirin decreased the frequency of all study end points. Aspirin decreased the frequency of CV deaths from 1.4% to 0.8% (RR 0.56, 95% confidence interval 0.31 to 0.99, p = 0.049). It is not certain if death due to stroke was part of this definition of CV deaths, because stroke was listed as a separate fatal event (the definition of CHD mortality in this meta-analysis includes death due to stroke). The combined end point of CV events, defined as nonfatal MI, nonfatal stroke, transient ischemic attack, angina pectoris, peripheral artery disease, and/or revascularization procedures, showed aspirin therapy to have an advantage (RR 0.23, p = 0.014).

In the WHS, apparently healthy women who were ≥45 years of age were randomly assigned to 100 mg of aspirin or placebo on alternate days and monitored for 10 years for a first major CV event (nonfatal MI, nonfatal stroke, or death from CV causes). There was a 17% decrease in the risk of stroke with aspirin compared with placebo (RR 0.83, 95% confidence interval 0.69 to 0.99, p = 0.04), with a significant decrease in risk of ischemic stroke, but a nonsignificant increase in the risk of hemorrhagic stroke.

The WHS was included in this 6-study meta-analysis to examine the consistency of the efficacy of aspirin from the combined analyses. The rationale and limitations of meta-analyses have been extensively reviewed. An excellent overview of a systematic step-by-step guide to performing a meta-analysis has also been published. The issues and possible sources of bias in meta-analysis studies are addressed in the following. Data from the 6 studies are readily available and interpretable, thus allowing analyses that incorporate the standard and rather recent approaches to meta-analysis.

**Methods**

The United States Preventive Services Task Force described the data collection and analysis from the first 5 primary prevention trials (BDT, PHS, TPT, HOT, and PPP) and, with the addition of the new data from the WHS, is the key source of data.

Because aspirin could have a differential effect on different aspects of CV disease, outcomes were classified as follows: (1) total CHD as nonfatal and fatal MI and death due to CHD; (2) nonfatal MI as confirmed MI that did not result in death; (3) total CV events as a composite of CV death, MI, or stroke; (4) stroke as ischemic or hemorrhagic stroke that may or may not have resulted in death; (5) CV mortality as death related to CHD or stroke; and (6) all-cause mortality as death related to any cause.

All 6 studies were screened for these outcomes. As presented in Table 1, all were randomized trials, the samples
ranged from 2,500 to almost 40,000, genders and subjects with various risk factors were included, and ages ranged from 40 to 84 years.

A separate meta-analysis was performed for each of the 6 end points because these are the primary outcomes of most, if not all, the included trials and the overall sample size is certainly adequate.

**Statistical analysis:** Data from the United States Preventive Services Task Force for each patient trial and data from the WHS were combined for analysis. For each previously described end point, a meta-analysis was performed for the comparison of aspirin with placebo/control. A summary odds ratio with 95% confidence interval was calculated. Calculation of the overall effect combining the 6 studies used the Mantel-Haenszel chi-square statistic on 1 degree of freedom. This test does not assume that patients in 1 study can be directly compared with those in another study, and it does not assume that any treatment effects are similar in different studies. It does not assume homogeneity but does take into account heterogeneity. The results were the same for fixed and random models (Meta Analysis, Biostat, Englewood, New Jersey). Heterogeneity was calculated using the chi-square test with n – 1 degrees of freedom, where n represented the number of studies contributing to the meta-analysis.

Forrest’s plots were used to assess if there was significant heterogeneity (defined as a p value < 0.01) and allowed assessment by considering the direction of the results. A weighting factor was also used that depends in part on the size of the study, which in turn affects the inverse variance formula that the Mantel-Haenszel procedure uses to calculate heterogeneity. The random-effects model also helps to further account for the heterogeneity across the studies, between study variations, and within-study variation or patient selection. However, given the summary data, the within-study variation is not easily assessed. The standard procedure for assessment of small study effects (i.e., a trend for relatively smaller studies to show larger treatment effects) has been the use of funnel plots using Egger’s test.16,17 There has been considerable discussion regarding the properties of this test.18-21 The technique of Macaskill et al20 has been used to adjust for this shortcoming. Also, see Harbord et al.22

**Results**

Among the trials in the analysis, there were 47,293 subjects who were treated with aspirin and 45,580 who received placebo/control.

Table 2 lists each study and indicates if statistical significance of aspirin over placebo was reached when using the odds ratio in any of the end points or groups of end points. Overall, these data provide clear evidence of the benefit of aspirin in total CHD, nonfatal MI, and total CV events and a positive trend for all-cause mortality; these effects are maintained with the addition of the data from the WHS.

The meta-analyses of all 6 predefined end points and the combined effect of aspirin on these end points are presented in Table 3. All odds ratios are < 1, suggesting at least a trend of decreased risk with aspirin than with placebo. Among subjects treated with aspirin, there was a significantly (p < 0.001) decreased risk of total CHD, nonfatal MI, and total CV events. These effects remained significant after adjustments for multiple comparisons (criteria are met for 0.05/6 = 0.008 required for significance for each outcome). There was significant heterogeneity (p < 0.01) for several of the end points listed in Table 3. This reflects the studies contributing to that end point, i.e., total CHD and nonfatal MI showed differing treatment effects.

The end points for total CHD, CV events, and stroke are shown in Figure 1; the remainder have the same format but are not included. For total CHD, Figure 1 shows that most studies have an odds ratio < 1, with an overall advantage of aspirin over placebo (odds ratio 0.772, p = 0.001). Figure 1 shows the composite of CV death, MI, and stroke, and an advantage of aspirin over placebo/control (odds ratio 0.852, p = 0.001). The odds ratios for stroke (Figure 1) are more variable, leading to the lack of overall significance (odds ratio 0.945, p = 0.336).

We had the ability to reexamine our results with respect to previous risk in studies that included TPT and PPP. The remainder of the studies showed no previous risk of CHD. The results were consistent with those presented in Table 3, all in favor of aspirin. For example, for total CHD, high risk

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**Table 2**  
Statistical significance of cardiovascular end points in the six primary prevention trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Total CHD</th>
<th>Nonfatal MI</th>
<th>CV Events</th>
<th>Stroke</th>
<th>CV Mortality</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHS</td>
<td>—</td>
<td>—</td>
<td>X</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BDT</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PHS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HOT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PPP</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>X</td>
<td>—</td>
</tr>
<tr>
<td>TPT</td>
<td>X</td>
<td>—</td>
<td>X</td>
<td>X</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

X = statistically significant odds ratios of aspirin versus placebo (p < 0.05). All are superior for aspirin effect over placebo.

**Table 3**  
Meta-analyses of predefined end points in the six primary prevention trials

<table>
<thead>
<tr>
<th>End Point</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
<th>p Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CHD</td>
<td>0.772</td>
<td>0.70–0.86</td>
<td>0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.755</td>
<td>0.67–0.85</td>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Total CV events</td>
<td>0.852</td>
<td>0.79–0.92</td>
<td>0.001</td>
<td>0.250</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.945</td>
<td>0.84–1.06</td>
<td>0.336</td>
<td>0.116</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.893</td>
<td>0.72–1.10</td>
<td>0.293</td>
<td>0.603</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.935</td>
<td>0.87–1.00</td>
<td>0.071</td>
<td>0.893</td>
</tr>
</tbody>
</table>
had an odds ratio equal to 0.775 (p = 0.001) and no previous risk had an odds ratio equal to 0.761 (p = 0.037). For nonfatal MI, high risk had an odds ratio equal to 0.647 (p = 0.009) and no previous risk had an odds ratio equal to 0.774 (p = 0.001). Likewise for studies of total CV events, high risk had an odds ratio equal to 0.735 (p = 0.001) and no previous risk had an odds ratio equal to 0.868 (p = 0.001). As presented in Table 3, results for stroke, CV mortality, and all-cause mortality, although with odds ratios in favor of aspirin, were not statistically significant for either risk group.

Discussion

Patients without any apparent history of CV disease were enrolled in the 6 large, randomized, primary prevention trials, and systematic analysis of the outcomes from these trials suggests that aspirin decreases the incidence of CHD events, nonfatal MI, and CV events. However, aspirin had no statistically significant effect on stroke, fatal CHD, or all-cause mortality. Whether there is an overall benefit of aspirin therapy in patients at low to moderate CV risk has been discussed elsewhere and is beyond the scope of this report. As presented in Table 3, results for stroke, CV mortality, and all-cause mortality, although with odds ratios in favor of aspirin, were not statistically significant for either risk group.

Based on the results of the meta-analysis, aspirin seems to decrease total CHD events, nonfatal MI, and CV events. The results are consistent with those of the Antithrombotic Trialists’ Collaborative Group, which conducted a meta-analysis to determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events. The meta-analysis compared antiplatelet therapy with a control and involved 287 randomized studies, some with antiplatelet regimens other than aspirin. Antiplatelet therapy decreased the combined outcome of any serious vascular event by about 25%, nonfatal MI by about 33%, nonfatal stroke by 25%, and vascular mortality by about 16%.

As shown in Figure 1, there was heterogeneity across studies for several outcomes. Possible sources of this heterogeneity include patient selection and randomization, baseline disease severity, management of intercurrent outcomes (such as bleeding, gastritis, and hypertension), treatment strategies, and patient characteristics. As presented in Table 1, there are such differences among the studies, as would be expected in this type of investigation. However, the overall difference between aspirin and placebo, as shown in this meta-analysis, is not affected by significant heterogeneity because similar results were obtained with the random-effects model, which accounts for the randomness of the effects across studies.

Before the addition of the WHS data to the 5 studies, the odds ratio for stroke was 1.035 in favor of placebo (p = 0.635); but after adding the WHS data, the odds ratio was 0.945 (p = 0.336) in favor of aspirin. For all-cause mortality, before the WHS, the odds ratio was 0.927 (p = 0.117) in favor of aspirin; after the addition of the WHS, the odds ratio was 0.935 (p = 0.071). There is clearly a trend of additional benefit in favor of aspirin as more results become available.
A limitation of our study, which generally is an accepted limitation, is that this is a meta-analysis from the literature results. Thus, we do not have the ability to do thorough cross-study checks that can be done using the raw data. Further, the overall size of our sample and the differing cohorts within each study lend convincing evidence to the advantage of aspirin over placebo or no aspirin for decreasing the risk of CV events in a range of patients. However, the benefits of primary prevention with aspirin need to be considered in relation to the potential risks on a patient basis. This meta-analysis supports the current recommendations for aspirin use when the benefits of a CV risk decrease outweigh treatment risks in most patients at higher coronary risk (10-year risk of CV disease ≥6%).\(^2\)\(^3\)


