Effect of Aspirin on Vascular and Nonvascular Outcomes

Meta-analysis of Randomized Controlled Trials

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Background: The net benefit of aspirin in prevention of CVD and nonvascular events remains unclear. Our objective was to assess the impact (and safety) of aspirin on vascular and nonvascular outcomes in primary prevention.

Data Sources: MEDLINE, Cochrane Library of Clinical Trials (up to June 2011) and unpublished trial data from investigators.

Study Selection: Nine randomized placebo-controlled trials with at least 1000 participants each, reporting on cardiovascular disease (CVD), nonvascular outcomes, or death were included.

Data Extraction: Three authors abstracted data. Study-specific odds ratios (ORs) were combined using random-effects meta-analysis. Risks vs benefits were evaluated by comparing CVD risk reductions with increases in bleeding.

Results: During a mean (SD) follow-up of 6.0 (2.1) years involving over 100,000 participants, aspirin treatment reduced total CVD events by 10% (OR, 0.90; 95% CI, 0.85-0.96; number needed to treat, 120), driven primarily by reduction in nonfatal MI (OR, 0.80; 95% CI, 0.67-0.96; number needed to treat, 162). There was no significant reduction in CVD death (OR, 0.99; 95% CI, 0.85-1.15) or cancer mortality (OR, 0.93; 95% CI, 0.84-1.03), and there was increased risk of nontrivial bleeding events (OR, 1.31; 95% CI, 1.14-1.50; number needed to harm, 73). Significant heterogeneity was observed for coronary heart disease and bleeding outcomes, which could not be accounted for by major demographic or participant characteristics.

Conclusions: Despite important reductions in nonfatal MI, aspirin prophylaxis in people without prior CVD does not lead to reductions in either cardiovascular death or cancer mortality. Because the benefits are further offset by clinically important bleeding events, routine use of aspirin for primary prevention is not warranted and treatment decisions need to be considered on a case-by-case basis.


WHILE META-ANALYSES TO DATE¹² HAVE SHOWN MODEST BENEFITS OF ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE (CVD), IT REMAINS UNCLEAR TO WHAT EXTENT THESE BENEFITS ARE OFFERED BY CLINICALLY IMPORTANT GUIDELINES FOR USE OF ASPIRIN IN PRIMARY PREVENTION OF CVD ARE BASED ON INFORMATION FROM TRIALS PUBLISHED UP TO 2005,⁵⁶ SINCE WHEN AT LEAST 3 ADDITIONAL STUDIES HAVE BEEN REPORTED.⁷⁹ IN THIS META-ANALYSIS WE THEREFORE AIMED TO PROVIDE AN UPDATED SYNTHESIS OF EVIDENCE REGARDING THE WIDER ROLE OF ASPIRIN IN PRIMARY PREVENTION, INCLUDING ITS EFFECT ON HITHerto UNDERINVESTIGATED OUTCOMES SUCH AS NONVASCULAR DISORDERS (ESPECIALLY CANCER), AND TO ASSESS WHETHER THE RISKS VS BENEFITS OF ASPIRIN TREATMENT VARY IMPORTANTLY ACCORDING TO KEY DEMOGRAPHIC OR PARTICIPANT CHARACTERISTICS.¹⁰⁻¹²

See Invited Commentary at end of article

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We searched the electronic databases PubMed and Cochrane Library from their inception to June 2011 using terms related to aspirin, coronary heart disease (CHD), CVD, cancer, nonvascular events, all-cause mortality, clinical trials, and primary prevention, without restriction to any language (Figure 1). This was supplemented by hand-searching their reference lists for additional studies. Our predefined inclusion criteria were randomized placebo-controlled trials that had included at least 1000 participants (without previous CHD or stroke, ie, primary prevention studies) and had at least 1 year of follow-up during which CHD and/or CVD outcomes (CHD, stroke, cerebrovascular disease, heart failure, and peripheral arterial disease [PAD]) were recorded as the main end points, and details were provided of bleeding events. As data on cancer and other nonvascular outcomes were generally unavailable in primary trial reports, we obtained relevant information from (1) subsequent trial reports that had published information on nonvascular events; (2) a recent individual-participant data meta-analysis of aspirin in mixed populations (ie, including both primary and secondary prevention populations); and using numbers provided therein to derive data on additional end points like noncancer, nonvascular death; (3) investigators of individual studies (2 studies [Hypertension Optimal Treatment Trial [HOT] and Physicians’ Health Study [PHS]] provided previously unpublished data on cancer). As nonvascular outcomes were generally reported as fatal events, risk estimates were calculated for cancer and other nonvascular mortality rather than incidence. Trials that enrolled subjects with pre-existing PAD were eligible for inclusion if they had been asymptomatic for this condition and had no history of CVD. Trials of secondary prevention or mixed primary and secondary prevention; pilot studies; and studies comparing aspirin with other antiplatelet agents instead of placebo were excluded. In case of multiple publications from the same source, we used information from the primary trial report unless stated otherwise. Thus, 9 trials involving 102,621 participants were eligible for the meta-analysis.

Three authors (S.W., R.S., and S.N.) independently abstracted the data (including demographic characteristics, number of patients and events, mean or median follow-up duration, and risk estimates), and discrepancies were resolved through discussion (S.R.K.S. and K.K.R.). For studies that reported combined clinical end points and at least 1 subsidiary point (eg, total CHD and either nonfatal MI or fatal CHD but not both), the number of events for the missing end point were calculated by simple subtraction (or addition, as relevant), assuming that these events did not overlap. Our primary efficacy end points were total CHD and total cancer mortality, with the secondary efficacy end points being subtypes of vascular disease, total CVD events, cause-specific death, and all-cause mortality. Because definitions for major bleeding events varied across studies, and since participant-level data were unavailable to allow reclassification according to standard criteria, we defined a category of clinically “nontrivial” bleeding (fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscus; bleeding requiring hospitalization and/or transfusion; or study-defined major bleeding regardless of source) as our composite primary safety end point. This roughly corresponds to type 2 or above of the Bleeding Academic Research Consortium definition for bleeding.©2012 American Medical Association. All rights reserved.
To assess the effect of aspirin we calculated study-specific unadjusted odds ratios (ORs) before combining them using random-effects meta-analysis (fixed-effect meta-analyses were conducted for comparison). We used calculated ORs instead of reported hazard ratios (HRs) to maximize available data on individual end points, and for consistency. Given the rare occurrence of many outcomes in primary prevention, we assumed that the calculated ORs would closely approximate reported HRs. Because individual studies differed with regard to various characteristics, heterogeneity was quantified using the I² statistic, and potential sources of heterogeneity were explored by subgroup analyses and metaregression. The I² statistic measures the proportion of overall variation in effect estimates that is attributable to between-study heterogeneity. Subgroup analyses involving grouping studies according to predefined characteristics and calculating stratum-specific ORs using random-effects meta-analysis. As analyses involved aggregate (and not individual-participant) data, it was not possible to study effect-modification by various participant-level characteristics. Metaregression was used instead to explore heterogeneity, using trial-level information. Crude event rates for aspirin and control groups were calculated using data on number of events and mean follow-up time (when mean follow-up was unavailable, median duration was used instead). To contextualize net benefit due to aspirin treatment, we compared rates of any statistically meaningful associations (CVD or nonfatal MI) with rates of bleeding. Mean baseline event rates for the combined study population were estimated by pooling study-specific control event rates for each outcome using random-effects meta-analysis. Numbers needed to treat (NNT) and harm (NNH) were derived by applying pooled ORs to the mean baseline event rates for the combined study population. Values of NNT and NNH provided herein represent the number of persons that need to be treated with aspirin for 6 years (the overall mean follow-up time in this study) to avert or incur, respectively, 1 event. Quality of studies was evaluated using a Delphi scoring system, which is based on the following: adequacy of randomization; allocation concealment; balance between randomized groups at baseline; a priori identification of inclusion criteria; presence or absence of blinding; use of intention-to-treat analyses; and reporting of point estimates and measures of variability for main outcomes. Potential publication bias was investigated using funnel plots and the Egger test. All P values reported are 2-sided; P < .05 was considered statistically significant. Statistical analyses were performed using Stata (version 10.1) software (StataCorp).  

RESULTS

STUDY POPULATION

Nine good-quality randomized controlled trials of aspirin for primary prevention of CVD including 102,621 participants were eligible (Figure 1; Table; and eTable 1 [http://www.archinternmed.com]). Most studies were conducted in Western populations and tended to include occupational groups (mainly health professionals). Numbers needed to treat (NNT) and harm (NNH) provided herein represent the number of persons that need to be treated with aspirin for 6 years (the overall mean follow-up time in this study) to avert or incur, respectively, 1 event. Quality of studies was evaluated using a Delphi scoring system, which is based on the following: adequacy of randomization; allocation concealment; balance between randomized groups at baseline; a priori identification of inclusion criteria; presence or absence of blinding; use of intention-to-treat analyses; and reporting of point estimates and measures of variability for main outcomes. Potential publication bias was investigated using funnel plots and the Egger test. All P values reported are 2-sided; P < .05 was considered statistically significant. Statistical analyses were performed using Stata (version 10.1) software (StataCorp).  

EFFECTS OF ASPIRIN ON VASCULAR AND NONVASCULAR OUTCOMES

Aspirin treatment was associated with a significant 10% reduction in risk of total CVD events (OR, 0.90; 95% CI, 0.85-0.96), largely owing to a 20% reduction in risk of nonfatal MI (OR, 0.80; 95% CI, 0.67-0.96) (Figure 2). There was no beneficial effect on fatal MI (OR, 1.06; 95% CI, 0.83-1.37), stroke (OR, 0.94; 95% CI, 0.84-1.06), or CVD death (OR, 0.99; 95% CI, 0.85-1.15). Modest, but nonsignificant, reductions were observed for total CHD (OR, 0.86; 95% CI, 0.74-1.01), total nonvascular mortality (OR, 0.92; 95% CI, 0.85-1.00), and all-cause mortality (OR, 0.94; 95% CI, 0.88-1.00), although there was no convincing evidence of benefit with regard to cancer mortality (OR, 0.93; 95% CI, 0.84-1.03). By contrast, there was a 70% excess risk of total bleeding events (OR, 1.70; 95% CI, 1.17-2.46) and a higher than 30% excess risk of nontrivial bleeding events (OR, 1.31; 95% CI, 1.14-1.50) in people receiving aspirin (eTable 3 contains details of definitions for bleeding). Qualitatively similar findings were observed in analyses restricted to studies of daily aspirin use (ie, after excluding Women’s Health Study [WHS]13 and PHS15), except that the risk of non-trivial bleeding was even higher in these studies (OR, 1.48; 95% CI, 1.17-1.86; eFigure 1). Considerable heterogeneity was observed for the ORs for major efficacy and safety end points (Figure 2 and eFigure 2), which could not be explained by reported characteristics (Figure 3 and eFigures 3-5). The risk of CVD events in people treated with aspirin was, however, lower at an older age (eFigure 6), and that of nontrivial bleeding was somewhat higher at a younger age and at higher systolic blood pressure (eFigure 5). Contrary to previous re-
Table. Characteristics of Individual Trials Contributing to the Current Analysis

<table>
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<th>Source</th>
<th>Location</th>
<th>Year</th>
<th>No. of Participants</th>
<th>Age, Mean (SD), y</th>
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<th>Diabetes, %</th>
<th>Smokers, %</th>
<th>SBP, Mean (SD), mm Hg</th>
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<td>2</td>
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<tr>
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<td>170</td>
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<tr>
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<td>13</td>
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<tr>
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<td>135</td>
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<td>28</td>
<td>3</td>
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<td>147.5</td>
</tr>
</tbody>
</table>

Total or Mean (SD) 102 621 57.3 (4.1) 46 8 16 138 (17)

Abbreviations: AAA, Aspirin for Asymptomatic Atherosclerosis Trial9; BDS, British Doctors Study24; HOT, Hypertension Optimal Treatment Trial14; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial8; NS, not stated; PHS, Physicians’ Health Study15; POPADAD, Prevention of Progression of Arterial Disease and Diabetes Trial7; PPP, Primary Prevention Project26; SBP, systolic blood pressure; TPT, Thrombosis Prevention Trial25; WHS, Women’s Health Study.13

Aspirin dose, schedule, and formulation distinguished the trials. In general, trial participants were aged 50 to 80 years and were randomly assigned to aspirin or placebo for an average of 6 to 10 years. Approximately 6% of participants were women. Diabetes was present in 2% to 22% of the study populations (JPAD8 and POPADAD7), or people with diabetes (JPAD8 and POPADAD7) or asymptomatic PAD (POPADAD7 and POPADAD8) and aspirin for asymptomatic atherosclerosis trial [AAA9]), or health care professionals (British Doctors Study [BDS],9 PHS,13 and WHS13) were excluded (eTable 4). Results were also similar when fixed-effect meta-analysis was used instead of random-effects models. There was no evidence of publication bias (Egger test P value > .05 for all major outcomes; eFigure 8).

SENSITIVITY ANALYSES

The effect of aspirin on nonfatal MI or total CVD events was unrelated to its average daily dose and was more pronounced in trials published before 2000 (compared with more recent studies; Figure 3). Findings were comparable when studies conducted exclusively in non-Western populations (JPAD8), or people with diabetes (JPAD8 and POPADAD7) or asymptomatic PAD (POPADAD7 and POPADAD8) and aspirin for asymptomatic atherosclerosis trial [AAA9]), or health care professionals (British Doctors Study [BDS],9 PHS,13 and WHS13) were excluded (eTable 4). Results were also similar when fixed-effect meta-analysis was used instead of random-effects models. There was no evidence of publication bias (Egger test P value > .05 for all major outcomes; eFigure 8).

COMPARATIVE MERITS OF ASPIRIN

The net benefit due to aspirin treatment (expressed as a difference between absolute event rates in the placebo and aspirin treatment arms) for both nonfatal MI and total CVD events increased proportionately with background event rates for these outcomes, although the benefit appeared to be more modest for CVD than nonfatal MI (Figure 4). Such benefits were offset by increased rates of nontrivial bleeding, even though for nonfatal MI there was a suggestion that at high baseline event rates there may be net benefit in favor of aspirin prophylaxis. The NNT to avoid 1 nonfatal MI event over 6 years was 162 (NNT was 120 to avoid 1 CVD event over the same period). By comparison, the NNT for nonvascular death was 292 (247 for cancer death), and at least 1 nontrivial bleeding event was caused for every 73 persons treated with aspirin for approximately 6 years.
This meta-analysis provides the largest evidence to date regarding the wider effects of aspirin treatment in primary prevention and contextualizes the relevance of aspirin prophylaxis by comparing CVD risk reduction against concomitant elevation in risk of bleeding. Unlike previous studies, the findings reported herein do not suggest a protective role for aspirin against cancer mortality in people at low-to-moderate risk for CVD events.

Available data also suggest that the principal cardiovascular effect of aspirin in primary prevention is on nonfatal MI with no real benefit with regard to fatal MI, stroke, or CVD death. Even these benefits are considerably offset by an elevated risk of bleeding (NNT for nonfatal MI of 162 vs NNH for nontrivial bleed of 73). Although our data failed to conclusively identify subgroups of participants likely to benefit from aspirin treatment, the results nevertheless suggest an increased risk of nontrivial bleeding in individuals receiving daily (vs alternate day) aspirin treatment, with a particularly unfavorable risk to benefit ratio for individuals at lower baseline CVD risk. Since it may be argued that events such as MI are potentially more serious compared with bleeding, both patients and physicians should carefully consider the relative merits of daily aspirin treatment in primary prevention.

However, modest, nonsignificant reductions in nonvascular death and all-cause mortality were observed, with questionable benefits...
Figure 4. Comparison of risk vs benefit due to aspirin treatment for primary prevention of cardiovascular disease. A, Plot of absolute risk difference in relation to background (ie, placebo) event rate for main outcomes. B, Plot comparing absolute number of nontrivial bleeding events caused vs absolute number of nonfatal MI events averted. C, Plot comparing absolute number of nontrivial bleeding events caused vs absolute number of total CVD events averted. In each of the panels, data points and associated labels correspond to individual studies, while straight lines represent fitted values. In panel A, the x-axis represents the background (ie, placebo) event rate for each of the outcomes of interest (nonfatal MI, total CVD, and nontrivial bleed), whereas the y-axis shows risk difference for these outcomes (total number of adverse events caused in case of nontrivial bleed events). In panels B and C, the x-axis shows the absolute number of events averted for nonfatal MI or total CVD, respectively, in each study plotted against the absolute number of nontrivial bleed events caused in the same studies. See Abbreviations footnote in the Table for a list of the trial names and reference citations.
settings, aspirin may add little extra value to other CVD risk reduction strategies that target lipid levels, blood pressure, and smoking, especially in low-risk individuals.

On the other hand, aspirin may be associated with net harm owing to increased potential for bleeding. Current guidelines for primary prevention advocate widespread use of aspirin in people at increased risk for CVD.33,34 Others have even suggested regular prophylaxis in people above a certain age, either singly35 or in combination with other agents.36 However, such strategies require closer scrutiny because aspirin cannot be compared with either statins or blood pressure–lowering agents with regard to its effects on CVD death. Hence, based on our findings of a marginal benefit on nonfatal MI, a nonsignificant effect on cancer death, and a significantly increased risk of clinically relevant bleeding, it is perhaps timely to re-appraise existing guidelines for aspirin use in primary prevention. Our data additionally highlight the need for more robust evidence in specific subgroups of participants,37,38 since current guidelines39 are based on limited evidence in different subgroups. Future studies should therefore aim to assess the impact of low-dose, alternate-day aspirin treatment on both vascular and nonvascular outcomes, especially in specific subgroups of individuals40 and within diverse populations.41 Also, owing to the relatively short mean follow-up duration reported in this meta-analysis, longer-term studies may be warranted to clarify the precise role of aspirin in cancer prevention.

Despite obvious advantages, there are important limitations to our analyses. First, we were unable to harmonize outcome definitions across studies (especially for outcomes with high heterogeneity such as bleeding) and were further unable to quantify precisely the effect of aspirin treatment in clinically relevant subgroups. Nonetheless, we combined bleeding episodes that were unlikely to be trivial and conducted subgroup analyses using available summary information. Second, as data on cancer incidence were generally unavailable from published reports, we were only able to assess the relationship between aspirin treatment and cancer mortality. Although this may have somewhat underestimated this association, it may have in fact been beneficial for study validity because estimates based on mortality, rather than incidence, are less likely to be affected by ascertainment bias. Third, the effect of aspirin on cancer mortality could be evaluated using information from only 8 of 9 studies. Nevertheless, these results are fairly robust because the majority of primary prevention trials of aspirin were included in our analyses. Fourth, as we studied the effect of aspirin on multiple outcomes, some of the associations may be due to chance alone. However, as the risk estimates were largely consistent with previous reports,32 the scope of any artifactual associations is likely to be limited. Lastly, as most studies were performed in occupational groups in Western populations, findings of this meta-analysis may not be entirely generalizable.

In conclusion, we found rather modest benefits of aspirin treatment on nonfatal MI and total CVD events in primary prevention, while the effect on cancer mortality was nonsignificant. Because the benefits of aspirin treatment were accompanied by a significant increase in risk of bleeding, further study is needed to identify subsets of participants having favorable risk to benefit ratio for aspirin use in primary prevention and/or involving more high-risk participants. In the absence of such information, a reappraisal of current guidelines appears to be warranted, particularly in countries where a large number of otherwise healthy adults are prescribed aspirin, since a significant proportion of them may develop bleeding complications.42

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Author Contributions: Drs Seshasai and Ray had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Seshasai and Ray. Acquisition of data: Seshasai, Wijesuriya, Sivakumaran, Nethercott, and Ray. Analysis and interpretation of data: Seshasai, Wijesuriya, Sivakumaran, Nethercott, Erqou, Sattar, and Ray. Drafting of the manuscript: Seshasai and Ray. Critical revision of the manuscript for important intellectual content: Seshasai, Wijesuriya, Sivakumaran, Nethercott, Erqou, Sattar, and Ray. Statistical analysis: Seshasai and Erqou. Study supervision: Seshasai, Sattar, and Ray.

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