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Data Sources: MEDLINE, Cochrane Library of Clinical Trials (up to June 2011) and unpublished trial data from investigators.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

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WHILE META-ANALYSES to date[1,2] have shown modest benefits of aspirin for the primary prevention of cardiovascular disease (CVD), it remains unclear to what extent these benefits are offset by clinically important bleeding episodes. Emerging data from primary and secondary prevention trials also suggest significant reductions in cancer mortality in people receiving aspirin prophylaxis,[3] stimulating discussions for more widespread use of this agent among healthy individuals.[4] Current guidelines for use of aspirin in primary prevention of CVD are based on information from trials published up to 2005,[5,6] since when at least 3 additional studies have been reported.[7-9] 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]

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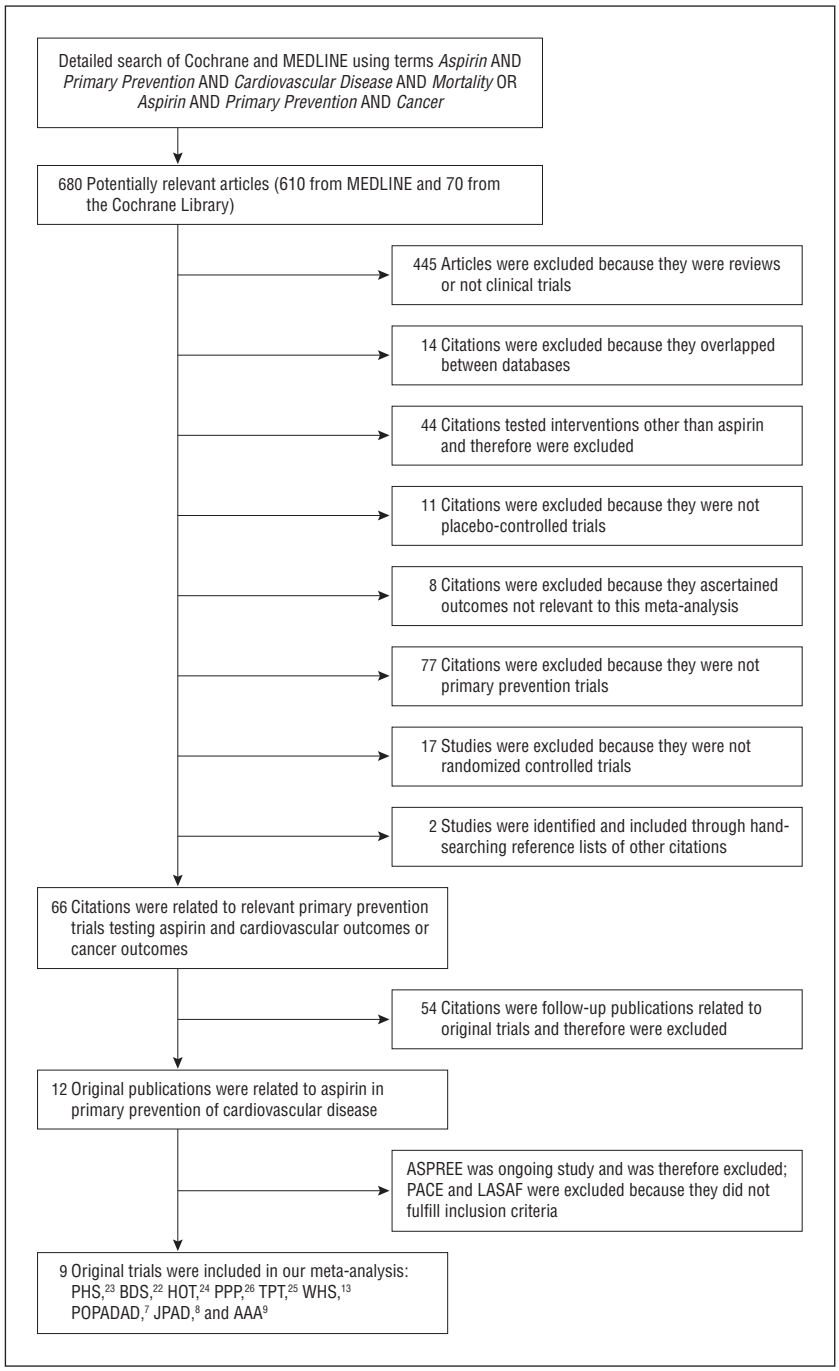

Figure 1. Details of literature review. See Abbreviations footnote in the Table for a list of the trial names. ASPREE indicates Aspirin in Reducing Events in the Elderly; LASAF, Low-Dose Aspirin, Stroke, Atrial Fibrillation; and PACE, Prevention With Low-Dose Aspirin of Cardiovascular Disease in the Elderly.

METHODS

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[13]; (2) a recent individual-participant data meta-analysis of aspirin in mixed populations[3] (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}[14] and Physicians' Health Study {PHS}[15]] 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,[16] pilot studies,[17] and studies comparing aspirin with other antiplatelet agents instead of placebo[18] 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 participants 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 end 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,[19,20] 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.[21]

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 I^2 statistic,[22] and potential sources of heterogeneity were explored by subgroup analyses and metaregression. The I^2 statistic measures the proportion of overall variation in effect estimates that is attributable to between-study heterogeneity. Subgroup analyses involved 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,[23] 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]).[7-9,14,15,24-27] Most studies were conducted in Western populations and tended to include occupational groups (mainly health professionals[15,24,27]). Pooled weighted mean (SD) age at baseline for all participants combined was 57 (4) years, and 46% (n = 47 070) were male. Although most trials selected participants at increased risk for CVD, they did not generally preselect individuals on the basis of diabetes (except Prevention of Progression of Arterial Disease And Diabetes Study [POPADAD][7] and Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial [JPAD][8]). Other characteristics, including risk factors for CVD, varied widely across studies.

FOLLOW-UP AND EVENTS

Over a mean (SD) follow-up of 6.0 (2.1) years (approximately 700 000 person-years at-risk) in 9 studies, 2169 CHD events were accrued, of which 1540 were nonfatal MI and 592 were fatal CHD events. One study[8] did not register any fatal MI events in the aspirin group; hence, 0.5 events were added to both treatment groups to calculate ORs. Other major outcomes included stroke (n = 1504); total CVD events (n = 4278); CVD death (n = 1285); nonvascular death (n = 2587); cancer death (n = 1512, 8 studies); noncancer, nonvascular death (n = 983, 8 studies); all-cause mortality (n = 3895); total bleeding events (n = 40 712); and nontrivial bleeding events (n = 10 049). Pooled event rates per 1000 person-years of follow-up in people randomized to aspirin vs placebo were 4.1 vs 5.1 for nonfatal MI; 1.9 vs 1.9 for fatal MI; 7.0 vs 8.1 for total CHD; 3.8 vs 4.0 for stroke; 12.8 vs 14.1 for total CVD events; 3.9 vs 4.0 for CVD mortality; 6.6 vs 7.2 for non-CVD death; 5.3 vs 5.9 for cancer death; 3.1 vs 3.2 for noncancer, nonvascular death; 11.0 vs 11.7 for all-cause mortality; 36.0 vs 21.2 for total bleeding events; and 9.7 vs 7.4 for nontrivial bleeding events. Losses to follow-up in individual studies are summarized in eTable 2.

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 PHS[15]), except that the risk of nontrivial 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

Source	Location	Year	No. of Participants	Age, Mean (SD), y	Male, %	Diabetes, %	Smokers, %	SBP, Mean (SD), mm Hg
BDS[24]	England	1988	5139	63.6	100	2	31	135.8
PHS[15]	US	1989	22 071	53.8	100	2	11	128.5
HOT[14]	Multiple	1998	18 790	61.5	53	8	16	170
TPT[25]	UK	1998	5085	57.5	100	NS	41	139
PPP[26]	Italy	2001	4495	64.4	42	17	15	145.1
WHS[13]	US	2005	39 876	54.6	0	3	13	127.3
POPADAD[7]	Scotland	2008	1276	60.3	44	100	31	145
JPAD[8]	Japan	2008	2539	64.5	55	100	21	135
AAA[9]	Scotland	2010	3350	61.6	28	3	32	147.5
Total or Mean (SD)			**102 621**	**57.3[a] (4.1)**	**46**	**8**	**16**	**138[a] (17)**

Source	Total Cholesterol, Mean (SD), mmol/L[b]	Aspirin Dose, mg, and Schedule	Aspirin Formulation	Concomitant Treatment[b]	All Participants, Duration of Follow-up, y[c]	Aspirin Arm, Duration of Follow-up, Person-years[d]	Placebo Arm, Duration of Follow-up, Person-years[d]
BDS[24]	NS	500 or 300 daily	Ordinary, soluble or effervescent (500 mg) or enteric coated (300 mg)	No	6.0	18 820	9470
PHS[15]	5.46	325 alternate day	Regular (most)	No	5.02	54 560	54 356
HOT[14]	6.1	75 daily	NS	Yes	3.8	35 716	35 686
TPT[25]	6.4	75 daily	Controlled release	Yes	6.4	8105	8071
PPP[26]	6.1	100 daily	Enteric coated	Yes	3.6	8014	8168
WHS[13]	5.2	100 alternate day	NS	Yes	10.1	201 333	201 414
POPADAD[7]	5.52	100 daily	NS	Yes	6.7	4275	4275
JPAD[8]	5.21	81 or 100 daily	NS	No	4.37	5515	5580
AAA[9]	6.2[a]	100 daily	Enteric coated	No	8.2	13 735	13 735
Total or Mean (SD)	**5.5 (0.5)**				**6.0 (2.1)**	**350 073**	**340 755**

Abbreviations: AAA, Aspirin for Asymptomatic Atherosclerosis Trial[9]; BDS, British Doctors Study[24]; HOT, Hypertension Optimal Treatment Trial[14]; JPAD, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial[8]; NS, not stated; PHS, Physicians' Health Study[15]; POPADAD, Prevention of Progression of Arterial Disease and Diabetes Trial[7]; PPP, Primary Prevention Project[26]; SBP, systolic blood pressure; TPT, Thrombosis Prevention Trial[25]; WHS, Women's Health Study.[13]

Conventional unit conversion factor: To convert cholesterol to milligrams per deciliter, divide by 0.0259.

[a] Represents weighted mean (SD).

[b] Concomitant treatments include agents other than anti-platelet drugs (eg, blood pressure-lowering medication), as in factorial trials.

[c] Follow-up duration shown for POPADAD and JPAD represents median follow-up, not mean. Also, total cholesterol values for POPADAD are median, not mean. Data on cholesterol measurements at baseline were missing in approximately 0.6% of all participants in the AAA study.

[d] Follow-up duration shown in person-years according to treatment arm was obtained directly from study reports for BDS and TPT, and was calculated based on numbers per group multiplied by mean (or median) follow-up time for other studies. In PHS, the reported duration of follow-up differed for various outcomes, and the numbers shown correspond to those for MI (including nonfatal and fatal MI).

ports,[28] we did not find any significant sex differences in treatment effect for total CVD events (eFigure 7). Lastly, no significant heterogeneity between studies was observed for nonvascular, cancer, and all-cause mortality ($P>.10$; Figure 2).

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 (JPAD[8]), or people with diabetes (JPAD[8] and POPADAD[7]) or asymptomatic PAD (POPADAD[7] and Aspirin for Asymptomatic Atherosclerosis Trial [AAA][9]), or health care professionals (British Doctors Study [BDS],[8] PHS,[15] and WHS[13]) 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 avert 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.

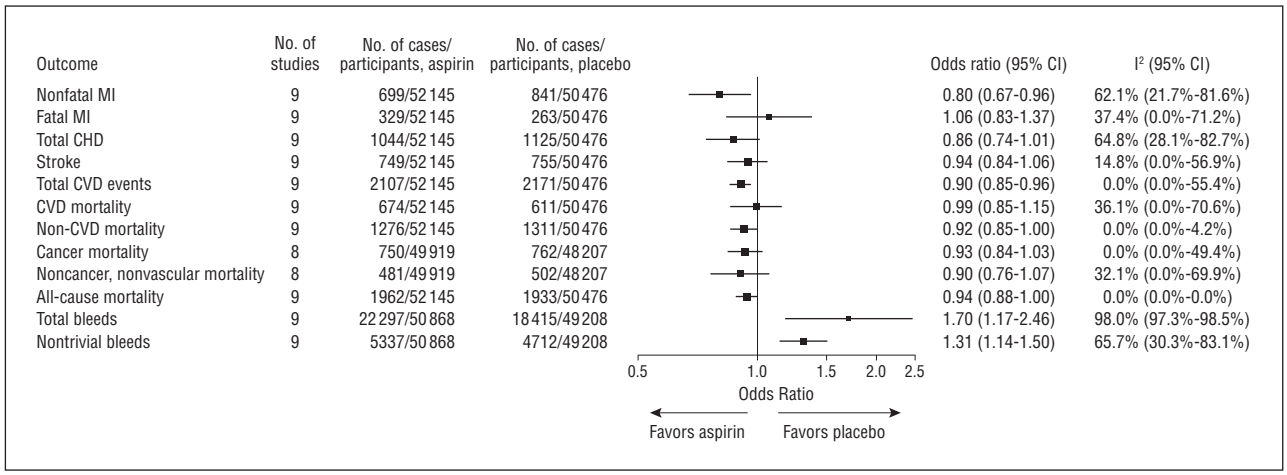

Figure 2. Effect of aspirin on vascular and nonvascular outcomes or death. CHD indicates coronary heart disease; CVD, cardiovascular disease; and MI, myocardial infarction.

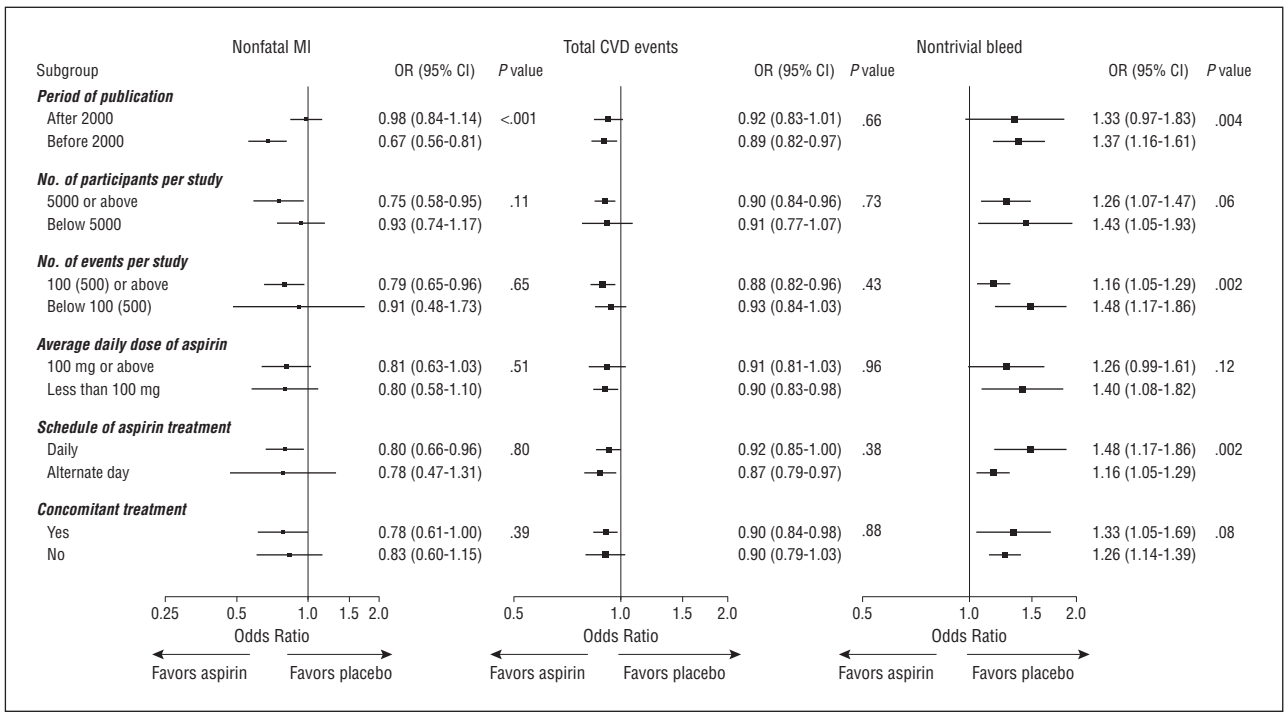

Figure 3. Effect of aspirin on nonfatal myocardial infarction (MI), total cardiovascular disease (CVD) events, and nontrivial bleeding events according to various study-level characteristics. For nonfatal MI, the number of events per study were categorized as 100 and above or below 100. For total CVD events and nontrivial bleeding, the corresponding categories were 500 and above or below 500. *P* values are shown for the overall test of heterogeneity between subgroups.

COMMENT

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,[3] 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

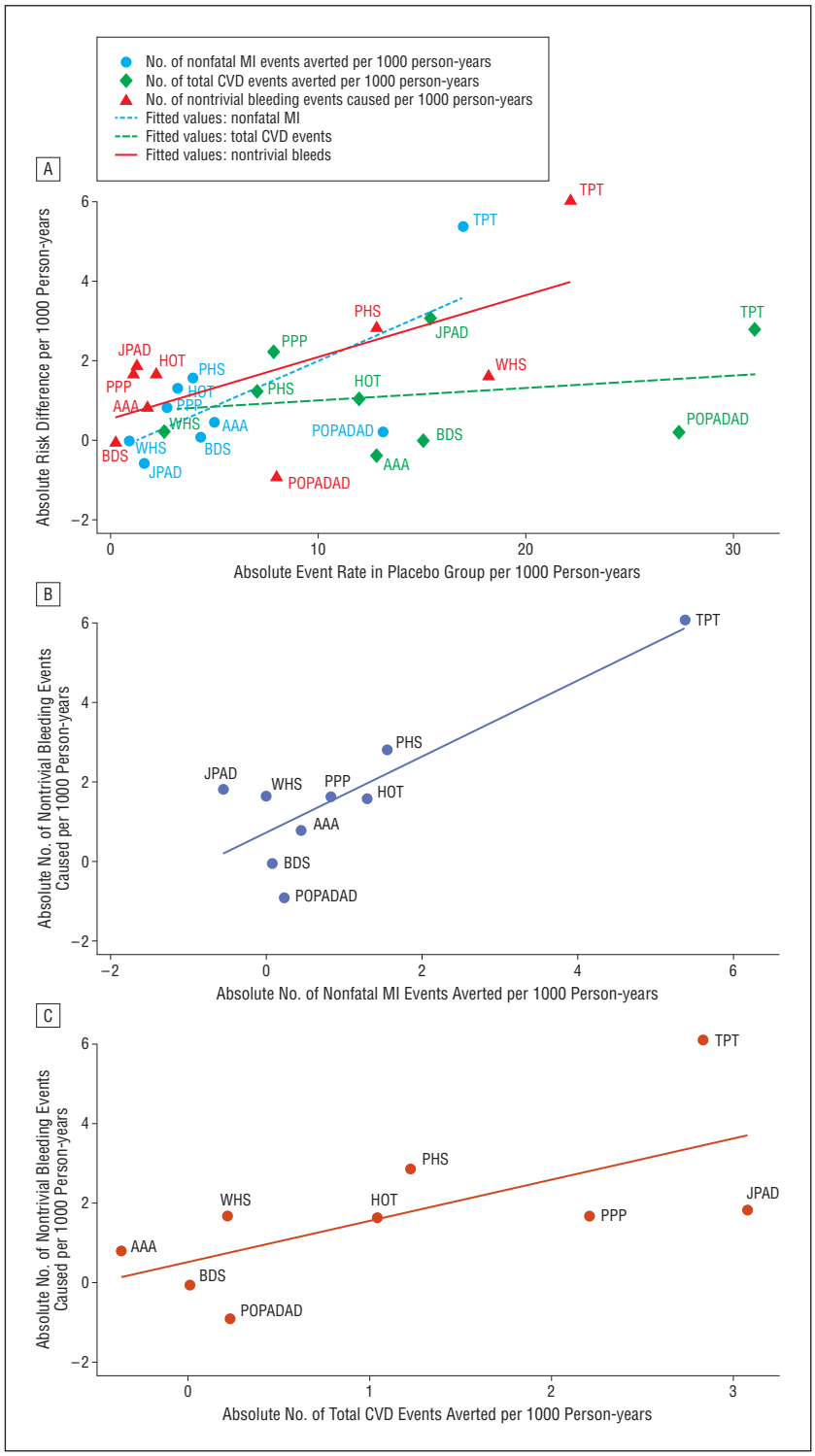

Figure 4. Comparison of risk vs benefit due to aspirin treatment for primary prevention of cardiovascular disease. A, Plot of absolute risk difference in relation to background (ie, placebo) event rate for main outcomes. B, Plot comparing absolute number of nontrivial bleeding events caused vs absolute number of nonfatal MI events averted. C, Plot comparing absolute number of nontrivial bleeding 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 events averted in case of nonfatal MI and total CVD, as against total number of adverse events caused in case of nontrivial bleeding). 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.

regarding cancer mortality. Although recent evidence suggests that aspirin reduces mortality from certain cancers,[3,29] this is based on information from both primary and secondary prevention studies. As background event rates for cancers and other chronic diseases may be different for participants with preexisting CVD, and since concomitant lifestyle or treatment decisions may alter risks associated with these outcomes, assessments of risk based on primary prevention trials is likely to be more informative. It has also been argued that the frequency of aspirin administration is an important determinant of cancer outcomes, with more sustained benefits with daily compared with alternate-day treatment.[3] However, we were unable to confirm these observations because cancer mortality failed to reach statistical significance even after excluding studies that had used alternate-day aspirin treatment (WHS[13] and PHS[15]) (OR, 0.88; 95% CI, 0.76-1.01). It is plausible that daily aspirin use may prompt earlier detection of cancers owing to investigation for bleeding, with apparent survival benefits (which may nevertheless be artifactual).

The findings of our analysis merit careful consideration in light of existing evidence regarding aspirin use in primary prevention. For instance, the magnitude of risk reduction observed for nonfatal MI and total CVD events is broadly consistent with some previous reports.[30] It has been suggested that the pharmacokinetics of aspirin may be different among men and women,[31,32] with consequent sex differences in efficacy. However, our analysis did not reveal any material differences in aspirin treatment effect by sex. Although these findings may be prone to ecological and other biases, they are in agreement with large-scale individual-participant data meta-analyses that showed lack of any important interaction by sex[30] for major CVD outcomes. Our analysis also showed that aspirin was no better than placebo for reducing nonfatal MI events in trials published after 2000, which may be ascribed to better treatments for CVD or underlying risk factors. This decline suggests that in contemporary primary prevention

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.[5,33,34] Others have even suggested regular prophylaxis in people above a certain age, either singly[35] 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 reappraise 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 guidelines[39] 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 individuals[40] 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,[30] 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 participant 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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Online-Only Material: The eTables and eFigures are available at http://www.archinternmed.com.

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