

Aspirin for the Primary Prevention of Cardiovascular Events: A Summary of the Evidence for the U.S. Preventive Services Task Force

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Background: The use of aspirin to prevent cardiovascular disease events in patients without a history of cardiovascular disease is controversial.

Purpose: To examine the benefits and harms of aspirin chemoprevention.

Data Sources: MEDLINE (1966 to May 2001).

Study Selection: 1) Randomized trials at least 1 year in duration that examined aspirin chemoprevention in patients without previously known cardiovascular disease and 2) systematic reviews, recent trials, and observational studies that examined rates of hemorrhagic strokes and gastrointestinal bleeding secondary to aspirin use.

Data Extraction: One reviewer read and extracted data from each included article and constructed evidence tables. A second reviewer checked the accuracy of the data extraction. Discrepancies were resolved by consensus.

Data Synthesis: Meta-analysis was performed, and the quantitative results of the review were then used to model the consequences of treating patients with different levels of baseline risk for coronary heart disease. Five trials examined the effect of aspirin on cardiovascular events in patients with no previous cardiovascular disease. For patients similar to those enrolled in the trials,

aspirin reduces the risk for the combined end point of nonfatal myocardial infarction and fatal coronary heart disease (summary odds ratio, 0.72 [95% CI, 0.60 to 0.87]). Aspirin increased the risk for hemorrhagic strokes (summary odds ratio, 1.4 [CI, 0.9 to 2.0]) and major gastrointestinal bleeding (summary odds ratio, 1.7 [CI, 1.4 to 2.1]). All-cause mortality (summary odds ratio, 0.93 [CI, 0.84 to 1.02]) was not significantly affected.

For 1000 patients with a 5% risk for coronary heart disease events over 5 years, aspirin would prevent 6 to 20 myocardial infarctions but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal bleeding events. For patients with a risk of 1% over 5 years, aspirin would prevent 1 to 4 myocardial infarctions but would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal bleeding events.

Conclusions: The net benefit of aspirin increases with increasing cardiovascular risk. In the decision to use aspirin chemoprevention, the patient's cardiovascular risk and relative utility for the different clinical outcomes prevented or caused by aspirin use must be considered.

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Cardiovascular disease, including ischemic coronary heart disease, stroke, and peripheral vascular disease, is the leading cause of morbidity and death in the United States (1). In 1997, the age-adjusted mortality rate due to coronary heart disease, cerebrovascular disease, and atherosclerotic disease was 194 per 100 000 persons, which is equivalent to more than 500 000 deaths per year (1). The estimated direct and indirect costs of coronary heart disease and stroke were \$145 billion for 1999 (2).

Although the benefit of aspirin for patients with known cardiovascular disease is well established (3), the question of whether aspirin reduces the risk for cardiovascular disease in persons without known cardiovascular disease is controversial. Two early randomized trials of aspirin in healthy men, the U.S. Physicians' Health

Study (PHS) and the British Male Doctors' Trial (BMD), had conflicting results regarding whether aspirin reduced the risk for myocardial infarction. Neither trial had sufficient power to precisely estimate major harms, such as gastrointestinal bleeding and hemorrhagic stroke (4, 5).

The results of these randomized, controlled trials were available to the members of U.S. Preventive Services Task Force at the time of their 1996 recommendation (4, 5). At that time, the Task Force found insufficient evidence to recommend for or against routine aspirin prophylaxis for the primary prevention of myocardial infarction in asymptomatic persons (6). Two additional large primary prevention trials were published in 1998, and another was reported in January 2001 (7-9). In light of the new evidence, the U.S. Preventive

Table 1. Summary of Primary Prevention Trials*

Variable	BMD	PHS	TPT	HOT	PPP
Reference	5	4	7	8	9
Year	1988	1989	1998	1998	2001
Location	United Kingdom	United States	United Kingdom	Worldwide	Italy
Duration of therapy, y†	5.8	5	6.8	3.8	3.6
Patients (women), n	5139 (0)	22 071 (0)	2540 (0)	18 790 (8831)	4495 (2583)
Aspirin dosage	500 mg/d	325 mg every other day	75 mg/d (controlled release)	75 mg/d	100 mg/d
Control	No placebo	Placebo	Placebo	Placebo	No placebo
Additional therapies	None	β-Carotene (50% of patients)	Warfarin‡	Felodipine with or without ACE inhibitor or β-blocker	Vitamin E
Included patients	Male physicians	Male physicians	Men at high risk for heart disease	Men and women with a diastolic blood pressure of 100 to 115 mm Hg	>1 major risk factor for CHD
Age	<60 y (46.9%); 60–69 y (39.3%); 70–79 y (13.9%)	Mean, 53 y (range, 40–84 y)	Mean, 57.5 y (range, 45–69 y)	Mean, 61.5 y (range, 50–80 y)	<60 y (29%); 60–69 y (45%); 70–79 y (24%)
Quality	Fair§	Good	Good	Good	Fair§

* ACE = angiotensin-converting enzyme; BMD = British Male Doctors' Trial; CHD = coronary heart disease; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Values given are means except for the TPT value, which is the median.

‡ Data from patients who received warfarin are not included in this table.

§ No placebo control or blinding.

Services Task Force sought to reassess the value of aspirin for the primary prevention of cardiovascular events. The Task Force's assessment was performed in partnership with the Agency for Healthcare Research and Quality, Rockville, Maryland, and investigators from the RTI-UNC Evidence-based Practice Center, Research Triangle Park, North Carolina. For this review, we examined three key questions: 1) Does aspirin chemoprevention in patients without known cardiovascular disease reduce the risk for myocardial infarction, stroke, and death? 2) Does aspirin chemoprevention increase major gastrointestinal bleeding, hemorrhagic strokes, or both? 3) What is the balance of benefits and harms for aspirin therapy in patients with different levels of risk for coronary heart disease? The analytic framework of the review can be found in **Appendix Figure 1** (available at www.annals.org).

METHODS

Identification of Relevant Trials

We searched MEDLINE from 1966 to May 2001 to identify studies examining aspirin's ability to prevent cardiovascular events and its likelihood of causing adverse effects. The literature search and data extraction are detailed in the Appendix (available at www.annals.org).

Quality Assessment

We assessed the quality of the trials that examined the benefits of aspirin therapy, considering methods of

randomization, blinding, analysis by intention to treat, follow-up rates, and crossover of assigned interventions. To look for differences in estimates of effect, we then performed meta-analyses using only the trials considered to be of good quality.

Modeling

We used our best estimates of the beneficial and harmful effects of aspirin chemoprevention to model its impact on populations of patients with different levels of risk for coronary heart disease. We estimated beneficial effects by using the odds ratios calculated from the meta-analyses; estimates of harmful effects were derived from other systematic reviews, supplemented by studies identified in our literature searches. We based our estimates on 1000 persons receiving aspirin for 5 years and used 95% CIs from the meta-analyses to produce plausible ranges around our point estimates. We also examined how these effects may differ for elderly persons, women, and patients with hypertension or diabetes.

Statistical Analyses

For individual trials, we calculated estimates of unadjusted odds ratios with 95% CIs (10). Because not all of the trials presented their outcomes using the same means of categorization, we contacted the investigators in some cases to determine the actual numbers of certain events and recalculated summary measures to improve

comparability. We performed meta-analysis using the DerSimonian and Laird random-effects model in RevMan (Cochrane Collaboration, Oxford, United Kingdom) (11). Heterogeneity was assessed by using graphs of the outcomes and the Mantel–Haenszel chi-square test.

DATA SYNTHESIS

Literature Searches

The results of our search strategy are shown in the Appendix (available at www.annals.org). We identified 5 randomized, controlled trials that had been designed to assess the efficacy of aspirin in the primary prevention of cardiovascular disease: the British Male Doctors' Trial (BMD), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment Trial (HOT), and the Primary Prevention Project (PPP) (4, 5, 7–9). We excluded 2 large trials that examined the effect of aspirin in patients with diabetes or with stable angina because more than 10% of the participants had definite or suspected vascular disease (12, 13). From our search for articles on adverse effects, we identified 9 articles that examined the effect of aspirin on gastrointestinal bleeding and hemorrhagic stroke (3, 14–21).

Trial Characteristics

The characteristics of the 5 randomized trials, which included a total of more than 50 000 patients, are shown in Table 1. The duration of the trials ranged from 3 to 7 years. Only 2 trials (HOT and PPP) included women. Aspirin dosage was 500 mg daily in BMD and 162 mg or less per day in the other 4 trials. Most participants were middle-aged, although 4 of the 5

trials included substantial numbers of patients who were 70 to 80 years of age.

Assessment of Study Quality

Overall, the quality of the trials examining the effectiveness of aspirin was high. All 5 trials concealed allocation of randomization. Researchers and participants were blinded in 3 trials (PHS, HOT, and TPT). In BMD and PPP, participants were not blinded and were not given placebo pills. Analyses in all trials were by intention to treat. Fewer than 1% of participants were lost to follow-up in BMD, PHS, and TPT, and 2.6% were lost to follow-up in HOT. In PPP, 7.7% of patients were lost to clinical follow-up, but data on vital status were obtained from census offices for 99.3% of the total sample.

During BMD, 39% of participants in the aspirin group discontinued therapy, primarily because of dyspepsia; 11% of participants assigned to no therapy began taking aspirin during the course of the trial. In contrast, in PHS, 14% of participants crossed over to the opposing treatment groups but rates of gastrointestinal discomfort did not differ significantly in each group. In PPP, 19% of patients assigned to aspirin discontinued taking it (8% due to side effects) and 7% of patients assigned to “no aspirin” were taking aspirin at the trial's conclusion. Crossover rates were not explicitly reported in TPT and HOT, although approximately 50% of patients participating in TPT withdrew for unreported reasons. However, the rate of withdrawal in TPT did not differ between the treatment and control groups. On the basis of these features, we rated the quality of

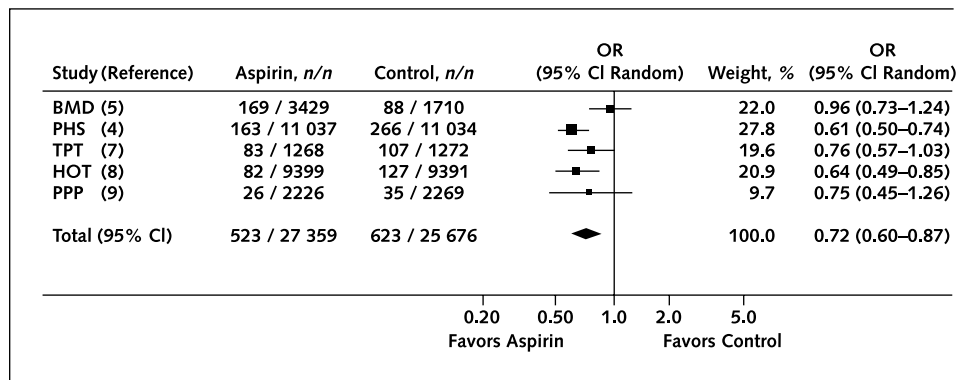
Table 2. Effect of Aspirin on Risk for Coronary Heart Disease in Primary Prevention Trials*

Trial (Reference)	Aspirin Events/Patients	Control Events/Patients	Odds Ratio (95% CI)	Duration of Therapy†	Annual Risk for a CHD Event among Control Patients	Approximate Vascular Events Avoided per 1000 Patients Treated per Year
	<i>n/n (%)</i>			<i>y</i>	<i>%</i>	<i>n</i>
BMD (5)	169/3429 (4.93)	88/1710 (5.15)	0.96 (0.73–1.24)	5.8	0.89	0.4
PHS (4)	163/11 037 (1.48)	266/11 034 (2.41)	0.61 (0.50–0.74)	5	0.48	1.9
TPT (7)	83/1268 (6.55)	107/1272 (8.41)	0.76 (0.57–1.03)	6.8	1.24	2.7
HOT (8)	82/9399 (0.87)	127/9391 (1.35)	0.64 (0.49–0.85)	3.8	0.36	1.3
PPP (9)	26/2226 (1.17)	35/2269 (1.54)	0.75 (0.45–1.26)	3.6	0.43	1.0

* BMD = British Male Doctors' Trial; CHD = coronary heart disease; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Values given are means except for the TPT value, which is the median.

Figure 1. Meta-analysis of total coronary heart disease events.



BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; OR = odds ratio; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial. The result of the chi-square test for heterogeneity was 8.07 ($P = 0.089$).

PHS, TPT, and HOT as “good” and the quality of BMD and PPP as “fair.”

Effect of Aspirin on Coronary Heart Disease

All trials had point estimates suggesting that aspirin prevented total coronary heart disease events, defined as nonfatal myocardial infarction or death due to coronary heart disease (fatal myocardial infarction or sudden death) (Table 2). In PHS and TPT, aspirin use was associated with increases in sudden death that did not reach statistical significance: 22 events with aspirin versus 12 events with placebo in PHS (odds ratio, 1.83 [95% CI, 0.91 to 3.71]) (4), and 18 events with aspirin versus 11 with placebo in TPT (odds ratio, 1.65 [CI, 0.78 to 3.51]) (22).

Meta-analysis of the 5 trials for the combined outcome of confirmed nonfatal myocardial infarction or death from coronary heart disease produced a summary odds ratio of 0.72 (CI, 0.60 to 0.87) (Figure 1). The Mantel–Haenszel test suggested possible heterogeneity ($P = 0.089$), reflecting the anomalous result of BMD. In that study, no difference was found in the rate of myocardial infarction between the intervention and control groups.

Mortality data for coronary heart disease (fatal myocardial infarctions and sudden death) from HOT and PPP were not reported separately in the main papers but were obtained from the authors (Hansson L. Personal communication, 2000; Roncaglioni C. Personal communication, 2001). Of the 5 trials, only PHS reported a statistically significant decrease in risk with aspirin (odds

ratio, 0.64 [CI, 0.42 to 0.99]). Cumulative mortality rates for coronary heart disease in the placebo group were low, ranging from 0.15% in HOT to 2.7% in BMD and TPT. Meta-analysis of the 5 trials found a summary odds ratio of 0.87 (CI, 0.70 to 1.09) (Figure 2, top). There was no significant heterogeneity in trial results ($P > 0.2$).

Effect of Aspirin on Stroke

It is difficult to interpret the overall effect of aspirin on stroke because the effect differs according to stroke subtype (Table 3). Data from secondary prevention trials suggest that aspirin prevents ischemic strokes but show that aspirin can also cause hemorrhagic stroke. The effect of aspirin on the total incidence of stroke depends on the patient's underlying risk for each stroke subtype (23). Overall stroke rates were lower than expected (based on age and risk factors) in all 5 primary prevention trials (Table 4). In each trial, control participants who had not been given aspirin had a less than 2% incidence of total strokes over 5 years. Because of the lower-than-expected stroke rates, the individual trials had limited statistical power to reliably detect the true effect of aspirin on stroke. Point estimates in PPP and TPT suggested modest decreases in total strokes, but CIs were wide (7, 23). In HOT, no effect of aspirin on overall rates of stroke was seen. In BMD and PHS, trends toward increased risk for stroke in aspirin-treated patients were observed but did not reach statistical significance (4, 5). The summary estimate (Figure 2, middle) showed no difference in total stroke overall (odds

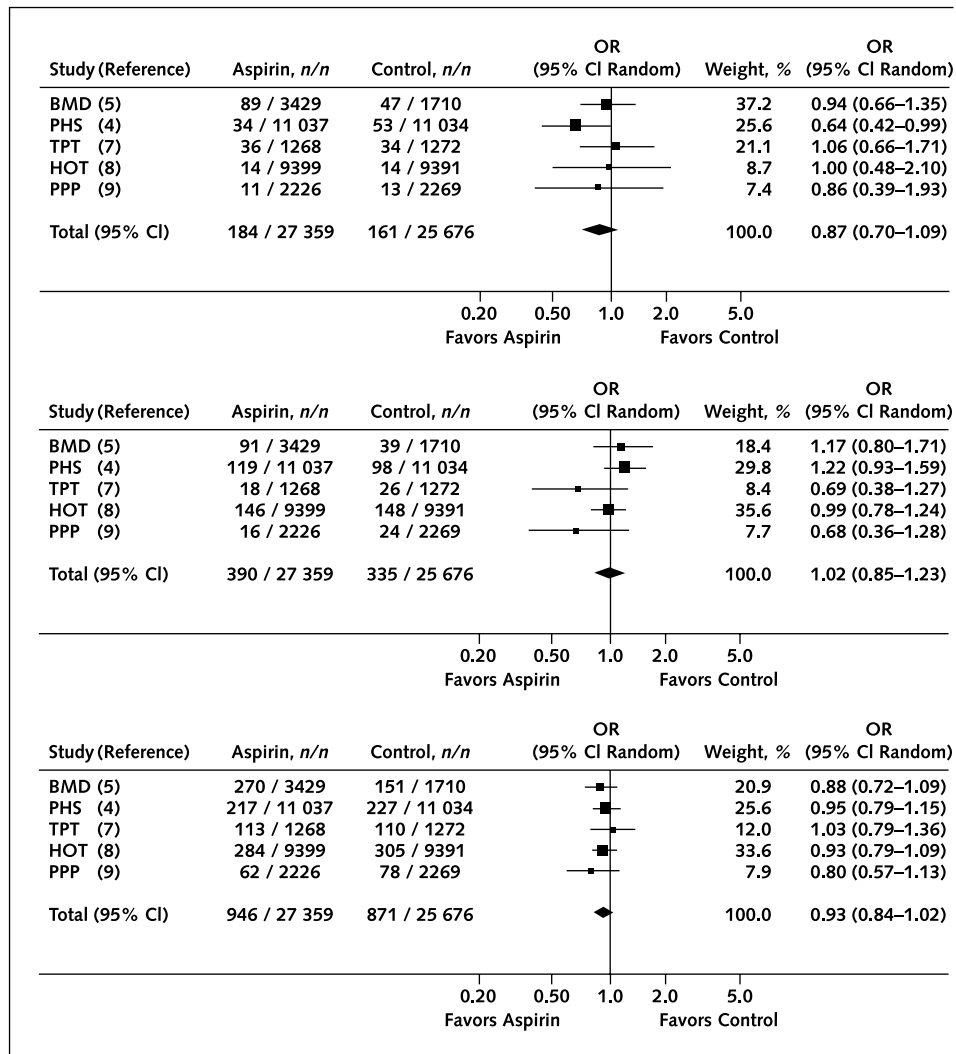
ratio, 1.02 [CI, 0.85 to 1.23]), and the results displayed no significant heterogeneity ($P > 0.2$).

The low number of strokes and the imperfect classification of stroke subtypes limited our ability to estimate the independent effect of aspirin on ischemic stroke in primary prevention settings. Rates of ischemic stroke were not specifically reported in HOT (8), and BMD did not use neuroimaging to differentiate ischemic from hemorrhagic strokes (5). In PHS, 91 ischemic strokes were seen with aspirin and 82 were seen with

placebo (odds ratio, 1.11 [CI, 0.83 to 1.50]) (5). In TPT, 10 ischemic strokes occurred in the aspirin group and 18 occurred in the placebo group (odds ratio, 0.55 [CI, 0.25 to 1.20]) (7). Fourteen ischemic strokes in the intervention group and 21 in the “no aspirin” group were reported in PPP (9).

Despite the uncertainty of stroke classification, Hart and colleagues (19) combined data from the first 4 primary prevention trials (4, 5, 7, 8) and concluded that aspirin appeared to have no effect on ischemic strokes in

Figure 2. Meta-analysis of the effect of aspirin on coronary heart disease mortality (top), fatal and nonfatal stroke events (middle), and all-cause mortality (bottom).



Results of the chi-square test for heterogeneity were 2.96 for coronary heart disease mortality, 5.36 for fatal and nonfatal stroke events, and 1.58 for all-cause mortality ($P > 0.2$ in all cases). BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; OR = odds ratio; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

Table 3. Estimates of the Role of Aspirin in Primary Prevention of Total Fatal and Nonfatal Stroke*

Trial (Reference)	Aspirin	Control	Odds Ratio (95% CI)	Duration of Therapy†	Annual Risk for	Vascular Events	Vascular Events
	Events/Patients	Events/Patients			Stroke among	Avoided per 1000	Caused per 1000
	n/n (%)			y	%	n	
BMD (5)	91/3429 (2.65)	39/1710 (2.28)	1.17 (0.80–1.71)	5.8	0.39	–	0.6
PHS (4)	119/11 037 (1.08)	98/11 034 (0.89)	1.22 (0.93–1.59)	5	0.18	–	0.4
TPT (7)	18/1268 (1.42)	26/1272 (2.04)	0.69 (0.38–1.27)	6.8	0.30	0.9	–
HOT (8)	146/9399 (1.55)	148/9391 (1.58)	0.99 (0.78–1.24)	3.8	0.41	0.1	–
PPP (9)	16/2226 (0.72)	24/2269 (1.06)	0.68 (0.36–1.28)	3.6	0.29	0.9	–

* BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Values given are means except for the TPT value, which is the median.

the middle-aged, relatively low-risk patients (relative risk, 1.03 [CI, 0.87 to 1.21]) (19).

Effect of Aspirin on All-Cause Mortality

None of the 5 trials found significant differences between aspirin-treated and control groups for all-cause mortality rates. Five-year mortality rates in the control groups of the individual trials ranged from 2% to 10%. The summary odds ratio for the effect of aspirin on all-cause mortality was 0.93 (CI, 0.84 to 1.02), consistent with a small or no reduction in all-cause mortality over 3 to 7 years (Figure 2, bottom).

Effectiveness of Aspirin Chemoprevention in Patient Subgroups

Most of the participants in the 5 randomized trials were middle-aged men. Limited data are available to examine whether the effect of aspirin differs in other demographic groups, including elderly persons, women, and persons with diabetes or hypertension. The following data come primarily from subgroup analyses and should be interpreted with caution.

Age

In PHS, aspirin reduced the relative risk for myocardial infarction for patients 70 to 84 years of age (relative risk, 0.49) as much as or more than it did for patients 60 to 69 years of age (relative risk, 0.46) and patients 50 to 59 years of age (relative risk, 0.58). In HOT, aspirin's effectiveness in patients older than 65 years of age (30% of the study sample) did not differ from its effect in those 50 to 64 years of age (24). In TPT, however, patients 65 to 69 years of age did not

benefit from aspirin (relative risk, 1.12) but younger patients did. Relative risks were 0.75 for patients 50 to 59 years of age and 0.61 for patients 60 to 64 years of age.

Sex

Only 2 of the 5 primary prevention trials included women (HOT and PPP). Kjeldsen and coworkers (24) performed a subgroup analysis of HOT to examine the influence of patient sex on the effectiveness of aspirin chemoprevention. Aspirin reduced the incidence of myocardial infarction in men (2.9/1000 patient-years in the aspirin group vs. 5/1000 patient-years in controls; relative risk, 0.58 [CI, 0.41 to 0.81]). However, its effect in women was smaller and not statistically significant (1.7/1000 person-years in the aspirin group vs. 2.1/1000 patient-years in controls; relative risk, 0.81 [CI, 0.49 to 1.31]). Sex differences in the effect of aspirin were not seen for stroke or all-cause mortality. In PPP, the investigators noted that women seemed to derive the same level of benefit from reduction of coronary heart disease as men, but specific data were not presented.

The question of whether sex modifies the effect of aspirin remains unclear. The Women's Health Study, a primary prevention trial that will test low-dose aspirin in approximately 40 000 patients, is expected to clarify risks and benefits among women (10).

Patients with Diabetes Mellitus

The proportion of patients with diabetes mellitus was small in each trial (PPP, 17%; HOT, 8%; PHS, 2%; BMD, 2%; TPT, 2%). In PHS, patients with diabetes derived greater benefit from aspirin than those without diabetes (relative risk, 0.39 vs. 0.60). Pooled

data from aspirin trials in secondary prevention settings (23) and a single trial in diabetic patients with and without coronary heart disease (12) also suggested that diabetic patients benefit as much or more from aspirin as nondiabetic patients.

Patients with Hypertension

The influence of hypertension on the effectiveness of aspirin chemoprevention has been examined in subgroup analyses. In TPT, Meade and Brennan (22) found that aspirin reduced total cardiovascular events in patients whose systolic blood pressure was less than 130 mm Hg (relative risk, 0.59) but not in patients whose systolic blood pressure was greater than 145 mm Hg (relative risk, 1.08). Patients with systolic blood pressure between 130 and 145 mm Hg also had reduced risk (relative risk, 0.68). In PHS, patients who were taking aspirin and had systolic blood pressure greater than 150 mm Hg had a relative risk of 0.65 for myocardial infarction, compared with relative risks of 0.55 for those with systolic blood pressure between 130 and 149 mm Hg and 0.52 for those with systolic blood pressure between 110 and 129 mm Hg (4). Significant reductions in coronary heart disease events were seen in HOT among patients with treated hypertension, but HOT did not have a comparison group of patients without hypertension (8).

On the basis of these data, aspirin seems to reduce risk for coronary heart disease in patients with treated hypertension, but its effects may be attenuated in patients with poorly controlled blood pressure.

Effect of Study Quality on Effectiveness of Aspirin

We performed an additional set of meta-analyses using only the 3 trials we rated as good (PHS, TPT,

HOT). The reduction in total coronary heart disease events was slightly larger (summary odds ratio, 0.65 [CI, 0.56 to 0.75]), but other outcomes were similar to our main analysis.

Adverse Effects of Aspirin Therapy

Hemorrhagic Stroke

The event rates for hemorrhagic strokes, including intracranial hemorrhage, were higher among aspirin-exposed participants than controls in BMD, PHS, and TPT, although these differences did not reach statistical significance in any single trial (Table 4) (4, 5, 7). In BMD, most strokes (>60%) were of unknown cause because computed tomography was not performed in most cases (5). In HOT and PPP, hemorrhagic strokes were almost equally common in the intervention and control groups (8, 9).

Two systematic reviews and meta-analyses have examined the effect of aspirin on the incidence of hemorrhagic stroke in the primary prevention trials. Hart and colleagues (19) pooled the results of the first 4 primary prevention studies and estimated that the relative risk for hemorrhagic stroke due to long-term aspirin use was 1.36 (CI, 0.88 to 2.1). Sudlow (25) recently performed a similar analysis using all 5 trials and reached a similar effect estimate (odds ratio, 1.4 [CI, 0.9 to 2.0]). In this analysis, the estimated annual excess risk with aspirin was 0.1 event per 1000 users.

He and coworkers (3) performed a meta-analysis of 16 trials (14 secondary prevention trials and the 2 older primary prevention trials [BMD and PHS]) that reported stroke subtype. Taken together, the trials involved more than 55 000 participants. Participants had a mean age of 59 years, and 86% were men. The mean

Table 4. Estimates of the Role of Aspirin in Hemorrhagic Stroke and Intracranial Hemorrhage*

Trial (Reference)	Aspirin Events/Patients	Control Events/Patients	Odds Ratio (95% CI)	Duration of Therapy	Annual Approximate Control Group Risk	Approximate Excess Bleeding Events per 1000 Patients Treated per Year	Approximate Bleeding Events Avoided per 1000 Patients Treated per Year
	n/n (%)			y	%	n	
BMD (5)	13/3429 (0.38)	6/1710 (0.35)	1.08 (0.41–2.85)	5.8	0.06	0.05	–
PHS (4)	23/11 037 (0.21)	12/11 034 (0.11)	1.92 (0.95–3.86)	5	0.02	0.2	–
TPT (7)	3/1268 (0.24)	2/1272 (0.16)	1.51 (0.25–9.03)	6.8	0.02	0.12	–
HOT (8)	14/9399 (0.15)	15/9391 (0.16)	0.93 (0.45–1.93)	3.8	0.04	–	0.03
PPP (9)	2/2226 (0.08)	3/2269 (0.13)	0.67 (NR)	3.6	0.04	–	0.12

* BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; NR = not reported; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

Table 5. Estimates of the Role of Aspirin in Gastrointestinal Bleeding*

Trial (Reference)	Type of Gastrointestinal Bleeding	Cumulative Incidence		P Value	Excess Bleeding Events per 1000 Patients Treated per Year	Fatal Gastrointestinal Bleeding Events	
		Aspirin Group	Control Group			Aspirin Group	Control Group
		%			← n →		
BMD (5)	Self-reported peptic ulcer disease	2.6	1.6	<0.05	1.7	3	3
PHS (4)	Upper gastrointestinal ulcers	1.5	1.3	0.08	0.4	1	0
TPT (7)	Major or intermediate bleeding†	1.7	0.8	NR	1.3	0	1
HOT (8)	Fatal and nonfatal major gastrointestinal bleeding events‡	0.8	0.4	NR	1.1	5	3
PPP (9)	Gastrointestinal bleeding§	0.8	0.2	NR	1.5	0	0

* BMD = British Male Doctors' Trial; HOT = Hypertension Optimal Treatment Trial; NR = not reported; PHS = Physicians' Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial.

† Major bleeding included fatal and life-threatening hemorrhages that required transfusion, surgery, or both. Intermediate episodes were bleeding events that prompted patients to notify research coordinators separately from routine questionnaires.

‡ Major bleeding was not defined.

§ Described as severe but nonfatal.

dosage of aspirin was 273 mg/d, and the mean duration of treatment was 37 months. The summary relative risk for hemorrhagic stroke with aspirin use was 1.84 (CI, 1.24 to 2.74). He and coworkers estimated that aspirin increased the absolute risk for hemorrhagic stroke by 12 events (CI, 5 to 20 events) per 10 000 persons over approximately 3 years, or about 0.4 excess event per 1000 users annually. This estimate is higher than that in Sudlow's meta-analysis, which included only primary prevention trials. He and coworkers also concluded that the absolute risk for hemorrhagic stroke did not vary significantly according to preexisting cardiovascular disease, mean age, sample size, dosage of aspirin, or study duration, although the statistical power to detect such differences was low because of the small number of total events.

The small number of primary prevention trials makes it difficult to examine the influence of other factors on the relationship between aspirin and hemorrhagic stroke. He and coworkers' systematic review did not find that age was an independent predictor of risk for hemorrhagic stroke, but the power of the review to detect such differences was low. In the large Stroke Prevention in Atrial Fibrillation II trial (26), advanced age was associated with an increased incidence of bleeding during aspirin therapy in patients with atrial fibrillation. The rate of intracranial hemorrhage with aspirin use was 0.2% per year in patients 75 years of age or younger and 0.8% per year in patients older than 75 years of age.

The question of whether there is a "safe" dose of aspirin with respect to hemorrhagic stroke has been ad-

ressed only in observational studies. A case-control study from Australia (27) examined the relationship between the use of aspirin or other nonsteroidal anti-inflammatory medications and the risk for hemorrhagic stroke. Reported use of low-dosage aspirin (<1225 mg/wk) was not associated with an increased risk for hemorrhagic stroke (odds ratio, 1.00 [CI, 0.60 to 1.66]) in multivariate risk-adjusted analyses. Larger amounts of aspirin were associated with hemorrhagic stroke (odds ratio, 3.05 [CI, 1.02 to 9.14]).

Gastrointestinal Bleeding

Aspirin increased the rates of gastrointestinal bleeding in all 5 primary prevention trials. Detection of events, definition of a "significant" bleeding event, and reporting of location of upper gastrointestinal bleeding varied across trials (Table 5).

Pooling the data on major extracranial bleeding from the 5 primary prevention trials, Sudlow estimated that aspirin increased the risk for major extracranial bleeding (odds ratio, 1.7 [CI, 1.4 to 2.1]). This translates to an excess risk for major, mostly gastrointestinal bleeding events of 0.7 (CI, 0.4 to 0.9) per 1000 patients treated with aspirin per year (25).

Several other systematic reviews have examined the risk for gastrointestinal bleeding with aspirin use (14-16, 28). Roderick and associates (15) performed a systematic review of 21 trials from the Antiplatelet Trialists' Collaboration (1990), all but 1 of which were secondary prevention studies. They estimated pooled odds ratios of 1.5 to 2.0 for gastrointestinal bleeding due

to aspirin. The risk for bleeding was greater in trials that used dosages exceeding 300 mg/d than in trials using lower dosages, but the difference was not statistically significant. Dickinson and Prentice (14) updated the Roderick review using data from trials that lasted more than 1 month. They determined that ongoing use of aspirin would produce an excess of two major gastrointestinal bleeding events per 1000 patient-years of exposure.

Recently, Derry and Loke (28) performed a systematic review and meta-analysis of trials published through 1999 that examined the risk for gastrointestinal hemorrhage with long-term (>1 year) aspirin use. They identified 24 randomized trials with a total of 66 000 participants and an average duration of 28 months. Aspirin use increased the odds of gastrointestinal hemorrhage (summary odds ratio, 1.68 [CI, 1.51 to 1.88]). The absolute risk difference was 1.05%. The authors estimated that treating 106 patients with aspirin for 28 months would lead to one excess episode of hemorrhage. Stalnikowicz-Darvasi performed a meta-analysis of 9 trials of low-dose aspirin prevention that had lasted at least 3 months (16); the pooled odds ratio for all gastrointestinal bleeding was 1.5 (CI, 1.3 to 1.7).

Derry and Loke (28) used meta-regression to examine the effect of aspirin dosage on the incidence of gastrointestinal hemorrhage and did not detect a statistically significant relationship (odds ratio, 1.015 [CI, 0.984 to 1.047] per 100-mg change in dose; $P > 0.2$). Cappelleri and colleagues (17) performed a meta-analysis and meta-regression to determine the effect of dosage on the risk for gastrointestinal bleeding with aspirin use among persons at high risk for vascular disease. They did not find a relationship between aspirin dose and risk for gastrointestinal bleeding but concluded that the likelihood of other gastrointestinal symptoms (for example, dyspepsia) increased with higher aspirin doses.

In a case-control study in Great Britain, Weil and coworkers (20) found that the risk for gastrointestinal bleeding was greater with all doses of aspirin compared with no usage but was higher with larger doses (odds ratios, 2.3 for 75 mg/d vs. 3.9 for 300 mg/d). Kelly and associates (18), in another case-control study, found an estimated relative odds of 2.6 for dosages less than 325 mg/d and 5.8 for larger doses. Enteric-coated or buffered preparations did not seem to reduce risk. Concomitant use of other nonsteroidal anti-inflammatory agents or anticoagulants further increased risk.

Table 6. Summary Estimates of the Effect of Aspirin*

Outcome	Odds Ratio (95% CI)
Benefits	
Myocardial infarction	0.72 (0.60–0.87)
CHD death	0.87 (0.70–1.09)
Total stroke	1.02 (0.85–1.23)
All-cause mortality	0.93 (0.84–1.02)
Harms	
Hemorrhagic stroke	1.4 (0.9–2.0)
Major gastrointestinal bleeding event	1.7 (1.4–2.1)

* CHD = coronary heart disease.

Silagy and colleagues (21) examined the adverse effects of low-dosage aspirin (100 mg/d) in a randomized, double-blind, placebo-controlled trial of 400 patients older than 70 years of age who did not have preexisting vascular disease. The reported absolute rate of any gastrointestinal bleeding in the aspirin group was 3% after 1 year. One case of bleeding duodenal ulcer required hospitalization for transfusion and emergency surgery. No gastrointestinal bleeding was reported for patients in the control group. Existing meta-analyses have not determined (3) or have not examined (28) whether age modifies the effect of aspirin on gastrointestinal hemorrhage, although cohort data suggest that the absolute risk for bleeding is higher in elderly persons (26).

Gastrointestinal Bleeding: Summary

Aspirin chemoprevention, even at low doses, seems to increase the risk for gastrointestinal bleeding by a factor of 1.5 to 2. The absolute excess risk for major bleeding events appears to be approximately 3 per 1000 middle-aged men receiving low-dose aspirin for more than 5 years. Higher rates (up to 2/1000 persons per year) are likely in elderly patients and perhaps among those using higher doses of aspirin.

Modeling a Risk Threshold for Aspirin Chemoprevention

Table 6 presents a summary of the effect estimates for the most important outcomes related to aspirin use. The estimates are based on the results of meta-analyses of data from the 5 primary prevention trials and therefore are most valid for middle-aged men (50 to 65 years of age) taking low-dosage aspirin (≤ 162 mg/d).

We used our best estimates of the beneficial and harmful effects of aspirin chemoprevention to model its impact on populations of patients with different levels of

Table 7. Estimated Benefits and Harms of Aspirin Therapy for Patients at Different Levels of Risk for Coronary Heart Disease Events*

Outcome	Estimated 5-Year Risk for CHD Events at Baseline		
	1%	3%	5%
Effect on all-cause mortality	No change	No change	No change
CHD events avoided, <i>n</i>	3 (1–4)	8 (4–12)	14 (6–20)
Ischemic strokes avoided, <i>n</i>	0	0	0
Hemorrhagic strokes precipitated, <i>n</i>	1 (0–2)	1 (0–2)	1 (0–2)
Major gastrointestinal bleeding events precipitated, <i>n</i>	3 (2–4)	3 (2–4)	3 (2–4)

* Estimates based on 1000 patients receiving aspirin for 5 years and a relative risk reduction of 28% for coronary heart disease (CHD) events in those who received aspirin. CHD events = nonfatal acute myocardial infarction, fatal CHD. Values in parentheses are 95% CIs. The following caveats apply to these estimates. 1) Reduction in CHD risk may be smaller in women, but data are limited. 2) For elderly persons, absolute risk for hemorrhagic stroke and major gastrointestinal bleeding may be two to three times higher in patients receiving aspirin; however, aspirin may provide benefit in elderly persons by reducing ischemic stroke, the incidence of which increases with age. Aspirin does not appear to improve incidence of ischemic stroke in middle-aged patients. 3) Risk for hemorrhagic stroke may be greater with larger doses of aspirin. 4) Aspirin may not prevent myocardial infarction in patients with uncontrolled hypertension (systolic blood pressure > 150 mm Hg). 5) Long-term outcomes (>5–7 years) are unknown. 6) Patients at high risk ($\geq 10\%$ 5-year risk) may derive greater benefit from aspirin, including a 15% to 20% reduction in ischemic stroke and all-cause mortality, because their risk is similar to that of patients with known CHD.

risk for coronary heart disease over 5 years. **Table 7** shows the net impact of low-dose aspirin chemoprevention on patients with different levels of risk. Treating patients with a moderately high risk (a 5-year risk of 5%) would prevent 14 events (range, 6 to 20). In low-risk patients, such as those with a 5-year risk of 1%, aspirin would prevent 3 events (range, 1 to 4). Low-dose aspirin is estimated to result in an excess of 1 hemorrhagic stroke (range, 0 to 2) and 3 major gastrointestinal bleeding events (range, 2 to 4) among 1000 persons treated in each group, independent of risk for coronary heart disease.

DISCUSSION

For patients without known cardiovascular disease who are similar to those enrolled in the 5 large primary prevention trials, our systematic review suggests that aspirin chemoprevention reduces myocardial infarction but has no effect on ischemic stroke or all-cause mortality over 5 years. Aspirin therapy also increases the risk for gastrointestinal bleeding and hemorrhagic stroke. Aspirin chemoprevention is probably beneficial for patients who have no previous diagnosis of cardiovascular

disease but are at high risk for developing coronary heart disease in the next 5 years. Conversely, patients at low risk for coronary heart disease probably do not benefit from and may even be harmed by aspirin because the risk for adverse events may exceed the benefits of chemoprevention (6, 29).

To aid in applying these general results to individual patients, we have attempted to define quantitatively the benefits and harms of aspirin at various levels of risk for coronary heart disease. The advantage of such an approach is that it allows a more specific and accurate discussion and consideration of the potential consequences of using or not using aspirin for each individual patient.

Utilization of our results in shared decision making with patients requires an estimation of a given patient's absolute risk for coronary heart disease as well as his or her willingness to accept the risks of low-dose aspirin to avoid coronary heart disease. Risk for future coronary heart disease events can be predicted from coronary risk algorithms (30). Factors used to estimate risk include sex, age, blood pressure, serum total cholesterol level (or low-density lipoprotein cholesterol level), high-density lipoprotein cholesterol level, diabetes mellitus, cigarette smoking, and left ventricular hypertrophy. Several easy-to-use risk assessment tools, most based on risk equations derived from the Framingham Heart Study, are available on the Internet (for example, at www.intmed.mcw.edu/clinical/heartrisk.html) or in printed form (30). Some tools calculate only 10-year risk estimates; in these cases, half of the 10-year estimate is a reasonable approximation of the 5-year risk for which we project our potential outcomes. Framingham data have recently been shown to generalize adequately to other populations (31). We have also provided a risk calculator at www.med-decisions.com to facilitate risk calculation.

Estimates of benefits and harms should be interpreted and compared cautiously. The principal beneficial effect of aspirin, a reduction in nonfatal myocardial infarction, cannot be directly equated to an adverse event, such as a stroke or gastrointestinal bleeding. We modeled outcomes over a period of 5 years because the trials included in our review ranged from 3 to 7 years in duration. However, outcomes from the use of aspirin chemoprevention will affect not only patients' current health status but also their future risk for coronary heart disease. For example, a nonfatal myocardial infarction

may produce a relatively small decrement in the patient's current health status but may also increase the future risk for a more disabling condition, such as recurrent myocardial infarction or congestive heart failure, and may lead to premature death.

The value that individual patients place on the outcomes affected by aspirin will vary. Decision analysts have measured mean values in representative populations. Augustovski and associates (32) used existing studies to estimate utility values as follows: nonfatal myocardial infarction, 0.88; disabling stroke, 0.50; non-disabling stroke, 0.75; and gastrointestinal bleeding, 0.97. Our estimates of expected event rates and these mean utility values can provide an initial framework for discussion with individual patients, who may weigh or value outcomes differently.

Others have attempted to quantitate the benefits and harms of aspirin therapy (19, 33). Sanmuganathan and colleagues (34) performed a meta-analysis of the first four primary prevention trials and reached similar estimates of the beneficial effects of aspirin. In their analysis, they combined data on harms into a single category of "major bleeding events" induced, and they calculated that the number of bleeding events induced equaled the number of cardiovascular events averted when the cardiovascular event rate was 0.22% per year. They further estimated that the upper end of the 95% confidence interval for this point estimate occurred at an event rate of 0.8% per year for cardiovascular disease; this is equivalent to an event rate of 0.6% per year for coronary heart disease. Sanmuganathan and colleagues concluded that aspirin was "safe and worthwhile" for persons whose risk for coronary heart disease events exceeded 1.5% per year and was "unsafe" for persons whose risk was less than 0.5% per year. However, their analysis treated the beneficial and harmful outcomes as equal in magnitude, an assumption that oversimplifies the clinical dilemma.

Augustovski and associates (32) used a Markov decision analysis model to consider the effect of low-dose aspirin for primary prevention in patients with different risk factor profiles. Effect estimates were based on the evidence available at the time of the analysis, which was before publication of the three most recent trials. Outcomes were measured as changes in quality-adjusted life-days. For 55-year-old patients, those at low risk (0 risk factors in men; 0 or 1 risk factor in women) were

harmed by aspirin therapy, whereas those at moderate to high risk (≥ 2 risk factors) seemed to benefit. However, because outcomes were presented in mean life-days gained or lost, it is difficult to translate their findings for use in counseling of individual patients.

On the basis of our review, we conclude that aspirin appears to reduce myocardial infarction but increases gastrointestinal and intracranial bleeding. The net effect of aspirin improves with increasing risk for coronary heart disease. Consideration of underlying risk for coronary heart disease, as well as the relative values patients attach to the main outcomes, can help patients and providers decide whether aspirin chemoprevention is warranted.

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APPENDIX: DETAILED DESCRIPTION OF SEARCH STRATEGY AND DATA EXTRACTION

Search Strategy

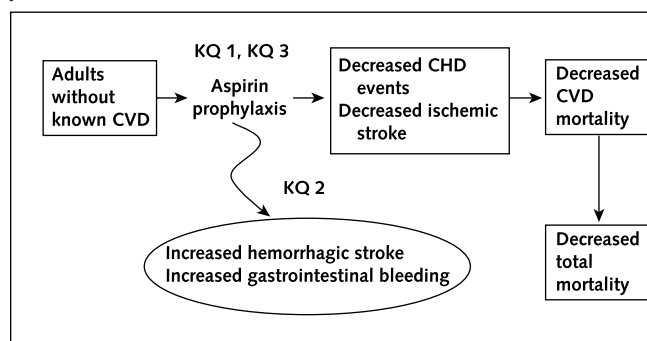
We used the following MeSH headings for the beneficial effects of aspirin: aspirin AND cardiovascular disease AND (randomized controlled trial or controlled clinical trial or randomized controlled trials or random allocation or double blind method or single blind method). The MeSH headings aspirin AND (gastrointestinal bleeding or cerebral hemorrhage) were used for the adverse effects of aspirin. We supplemented our basic search strategies by examining bibliographies from other relevant articles and systematic reviews and by seeking the advice of content experts. Our search strategy is detailed in **Appendix Figures 2 and 3**.

Inclusion Criteria

For studies examining the benefits of aspirin chemoprevention, we included randomized trials of at least 1 year in duration that met the following criteria: 1) compared aspirin with placebo or no aspirin; 2) included patients with no previous history of cardiovascular disease, including myocardial infarction, stroke, angina, transient ischemic attack, or peripheral vascular disease (trials in which >10% of participants had known vascular disease were excluded); and 3) measured the outcomes of myocardial infarction, stroke, and mortality (**Figure 1**).

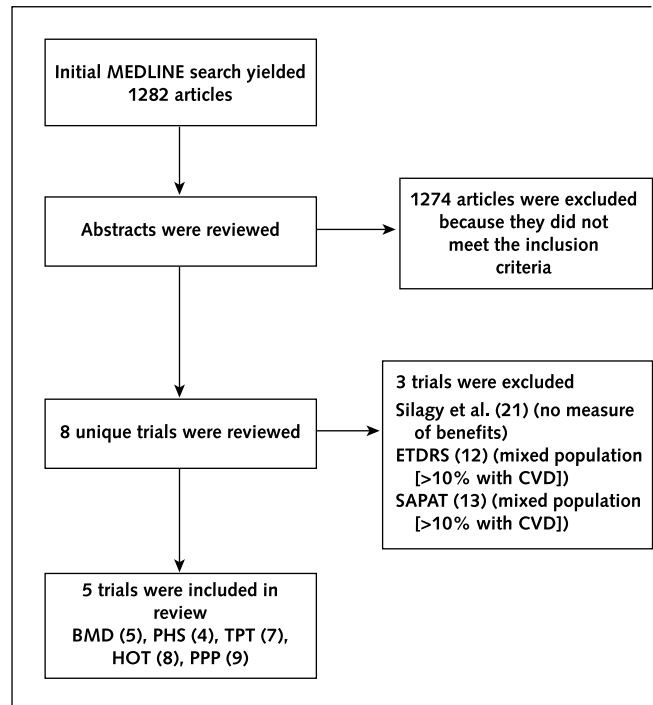
For harms data, we examined case-control studies, randomized trials, and systematic reviews or meta-analyses of randomized trials that examined rates of hemorrhagic stroke or gastrointestinal bleeding from aspirin use.

Appendix Figure 1. Analytic framework: aspirin to prevent cardiovascular events.



CHD = coronary heart disease; CVD = cardiovascular disease; KQ = key question. KQ 1: Does aspirin chemoprevention in patients without known cardiovascular disease reduce the risk for myocardial infarction, stroke, and death? KQ 2: Does aspirin chemoprevention increase major gastrointestinal bleeding, hemorrhagic strokes, or both? KQ 3: What is the balance of benefits and harms for aspirin therapy in patients with different levels of cardiovascular risk?

Appendix Figure 2. Search strategy: beneficial effects.



BMD = British Male Doctors' Trial; CVD = coronary vascular disease; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Trial; PHS = Physicians' Health Study; PPP = Primary Prevention Project; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial.

Data Extraction and Definition of Outcomes

Two reviewers examined all abstracts and excluded those that they agreed were clearly outside the scope of the review. The same reviewers then examined the full articles for the remaining studies and determined final eligibility by consensus. Two independent reviewers abstracted the included studies. Disagreements were resolved by consensus. Potentially beneficial outcomes examined were the efficacy of aspirin versus placebo in reducing the following events: 1) nonfatal acute myocardial infarction or death due to coronary heart disease, including fatal acute myocardial infarction or death from other ischemic heart disease; 2) fatal or nonfatal stroke; 3) total cardiovascular events (nonfatal acute myocardial infarction, death from coronary heart disease, and fatal or nonfatal stroke); and 4) all-cause mortality. Major harms examined were hemorrhagic stroke and major gastrointestinal bleeding.

Appendix Figure 3. Search strategy: harmful effects.

