Aspirin for the Primary Prevention of Cardiovascular Events: A Summary of the Evidence

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Epidemiolgy

Cardiovascular disease (CVD), including ischemic coronary heart disease (CHD), stroke, and peripheral vascular disease, is the leading cause of morbidity and mortality 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 people, equating to more than 500,000 deaths per year.[1] The estimated direct and indirect costs of CHD and stroke were $145 billion for 1999.[2]

Although the benefit of aspirin for patients with known CVD is well established,[3] the question of whether aspirin reduces the risk of CVD in people without known CVD is controversial. Two early randomized trials of aspirin in healthy men, the U.S. Physicians' Health Study (PHS) and British Male Doctors (BMD) trial, 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 first 2 randomized, controlled trials were available to the members of the 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 people.[6]

Two additional large primary prevention trials were published in 1998, and another was reported in January 2001.[7, 8, 9] In light of the new evidence, the U.S. Preventive 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 (AHRQ) and investigators from the RTI-UNC Evidence-based Practice Center. For this review, we

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The USPSTF recommendations based on this evidence review can be found in Aspirin for the Primary Prevention of Cardiovascular Events: Recommendations and Rationale (which precedes this chapter), available on the AHRQ Web site and through the AHRQ Publications Clearinghouse.

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examined 3 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 and/or hemorrhagic strokes? (3) What is the balance of benefits and harms for aspirin therapy in patients with different levels of CHD risk?

Methods

Identification of Relevant Trials

We searched MEDLINE® from 1966 to May 2001 to identify studies that examined 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.

Statistical Analyses

For individual trials, we calculated estimates of unadjusted odds ratios with 95% confidence intervals (CIs).[10] Because all of the trials did not all present 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 Reviewer Manager (RevMan).[11] Heterogeneity was assessed by using graphs of the outcomes and the Mantel-Haenszel chi-square test (Q).

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. We then performed meta-analyses using only the trials considered to be of good quality to look for differences in effect estimates.

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 CHD. 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 1,000 people 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 the elderly, women, and patients with hypertension or diabetes.

Results

Literature Searches

The results of our search strategy are shown in the Appendix. 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 on 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]

Studies Examining the Benefits of Aspirin Chemoprevention

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 dose 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 aged 70 to 80 years.

Table 1. Summary of primary prevention trials

Variable	BMD[5]	PHS[4]	TPT[7]	HOT[8]	PPP[9]
Year	1988	1989	1998	1998	2001
Location	United Kingdom	Unites States	United Kingdom	Worldwide	Italy
Duration of therapy, *y*[a]	5.8	5	6.8	3.8	3.6
Patients (women), *n*	5,139 (0)	22,071 (0)	2,540 (0)	18,798 (8,831)	4,495 (2,583)
Aspirin dosage	500 mg daily	325 mg every other day	75 mg daily (controlled-release)	75 mg daily	100 mg daily
Control	No placebo	Placebo	Placebo	Placebo	No placebo
Additional therapies	None	β-Carotene (50% of patients)	Warfarin[b]	Felodipine with or without ACE inhibitor or β-blocker	Vitamin E
Included patients CHD	Male physicians	Male physicians	Men at high risk for heart disease	Men and women with diastolic blood pressure of 100 to 115 mm Hg	>1 major risk factor for
Age	<60 years (46.9%); 60-69 years (39.3%); 70-79 years (13.9%)	Mean, 53 years (range 40-84 years)	Mean, 57.5 years (range 45-69 years)	Mean, 61.5 years (range 50-80 years)	<60 years (29%); 60-69 years (45%); 70-79 years (24%)
Quality	Fair[c]	Good	Good	Good	Fair[c]

[a]Values given are means except for the TPT value, which is the median.

[b]Data from patients who received warfarin are not included in this table.

[c]No placebo control or blinding.

Note: ACE indicates angiotensin-converting enzyme; BMD, British Male Doctors' Trial; CHD, coronary heart disease; HOT, Hypertension Optimal Treatment Trial; IHD, ischemic heart disease; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial.

Study Quality Assessment

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 the BMD trial, 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 the PHS trial, 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 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. Based on these features, we rated the quality of the PHS, TPT, and HOT trials as "good" and the quality of the BMD and PPP trials as "fair."

Effect of Aspirin on Coronary Heart Disease

CHD events. All trials had point estimates suggesting that aspirin prevented total CHD events, defined as nonfatal myocardial infarction (MI) or death due to coronary heart disease (fatal MI or sudden death; see 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 the PHS trial (OR 1.83; 95% CI, 0.91, 3.71),[4] and 18 events with aspirin versus 11 with placebo in the TPT trial (OR, 1.65; 95% 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 CHD produced a summary odds ratio of 0.72 (95% CI, 0.60 to 0.87) (Figure 1). The Mantel-Haenszel test suggested possible heterogeneity (chi square=8.07, P=0.089), reflecting the anomalous result of the BMD. In that study, no difference was found in the rate of myocardial infarction between the intervention and control groups.

CHD mortality. We also examined the effect of aspirin on CHD mortality. Mortality data for coronary heart disease (fatal myocardial infarctions and sudden death) from the HOT and PPP trials were not reported separately in the main papers but were obtained from the authors (Hannson L. Personal communication, 2000; Roncaglioni C. Personal communication, 2001). Of the 5 trials, only PHS reported a statistically significant decrease in risk with aspirin (OR, 0.64; 95% CI, 0.42 to 0.99). Cumulative CHD mortality rates 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 (95% CI, 0.70 to 1.09) (Figure 2). 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 for different types of stroke. 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

Table 2. Effects of aspirin on risk for coronary heart disease in primary prevention trials

Trial	Aspirin events/ patients (%)	Control events/ patients (%)	Odds ratio (95% CI)	Duration of therapy[a]	Annual risk for a CHD event among control patients	Approximate vascular events avoided per 1,000 patients treated per year
BMD[5]	169/3,429 (4.93)	88/1,710 (5.15)	0.96 (0.73 to 1.24)	5.8 years	0.89%	0.4
PHS[4]	163/11,037 (1.48)	266/11,034 (2.41)	0.61 (0.50 to 0.74)	5.0 years	0.48%	1.9
TPT[7]	83/1,268 (6.55)	107/1,272 (8.41)	0.76 (0.57 to 1.03)	6.8 years	1.24%	2.7
HOT[8]	82/9,399 (0.87)	127/9,391 (1.35)	0.64 (0.49 to 0.85)	3.8 years	0.36%	1.3
PPP[9]	26/2,226 (1.17)	35/2,269 (1.54)	0.75 (0.45 to 1.26)	3.6 years	0.43%	1.0

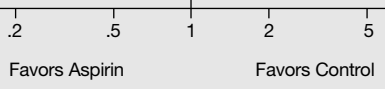
[a]Values given are means except for the TPT value, which is the median.

Note: BMD indicates 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.

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

Trial	Aspirin n/N	Control n/N	OR (95% CI Random)	Weight %	OR (95% CI Random)
BMD[5]	169/3,429	88/1,710		22.0	0.96[0.73,1.24]
PHS[4]	163/11,037	266/11,034		27.8	0.61[0.50,0.74]
TPT[7]	83/1,268	107/1,272		19.6	0.76[0.57,1.03]
HOT[8]	82/9,399	127/9,391		20.9	0.64[0.49,0.85]
PPP[9]	26/2,226	35/2,269		9.7	0.75[0.45,1.26]
Total (95%CI)	523/27,359	623/25,676		100.0	0.72[0.60,0.87]

Test for heterogeneity chi-square=8.07 df=4 *P*=0.089



Note: BMD indicates British Male Doctors' Trial; HOT, Hypertension Optimal Treatment Trial; 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).

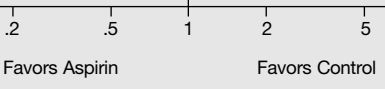
total incidence of stroke depends on the patient's underlying risk for each stroke subtype.[23] Overall stroke rates were lower than expected (based on age and risk factors) in all 5 primary prevention trials (Table 4). In each trial, control participants who had not been given aspirin had a less than 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. The PPP and TPT trials had point estimates suggesting modest decreases in total strokes, but CIs were wide.[7,23] In HOT, no effect of aspirin on overall rates of stroke was seen. The BMD and PHS trials observed trends toward increased risk for stroke in aspirin-treated patients that did not reach statistical significance.[4,5] The summary estimate (Figure 3) showed no difference in total stroke overall (OR, 1.02; 95% CI, 0.85 to 1.23). 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 aspirin's independent effect on ischemic stroke in primary prevention settings. HOT did not specifically report rates of ischemic stroke,[8] and BMD did not use neuroimaging to differentiate

Figure 2. Meta-analysis of the effect of aspirin on coronary heart disease mortality

Trial	Aspirin n/N	Control n/N	OR (95% CI Random)	Weight %	OR (95% CI Random)
BMD[5]	89/3,429	47/1,710		37.2	0.94[0.66,1.35]
PHS[4]	34/11,037	53/11,034		25.6	0.64[0.42,0.99]
TPT[7]	36/1,268	34/1,272		21.1	1.06[0.66,1.71]
HOT[8]	14/9,399	14/9,391		8.7	1.00[0.48, 2.10]
PPP[9]	11/2,226	13/2,269		7.4	0.86[0.39,1.93]
Total (95%CI)	184/27,359	161/25,676		100.0	0.87[0.70,1.09]

Test for heterogeneity chi-square=2.96 df=4 *P*=0.57



Note: BMD indicates British Male Doctors' Trial; HOT, Hypertension Optimal Treatment Trial; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial. The result of the chi-square test for heterogeneity was 2.96 (*P*=0.57).

ischemic from hemorrhagic strokes.[5] The PHS trial reported 91 ischemic strokes with aspirin and 82 with placebo (OR, 1.11; 95% CI, 0.83 to 1.50).[4] In TPT, 10 ischemic strokes occurred in the aspirin group and 18 occurred in the placebo group (OR, 0.55; 95% CI, 0.25 to 1.20).[7] The PPP trial had 14 ischemic strokes in the intervention group and 21 in the "no aspirin" group.[9]

Despite the uncertainty of stroke classification, Hart et al[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 the middle-aged, relatively low-risk patients (RR, 1.03; 95% CI, 0.87 to 1.21).[19]

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 (95% CI, 0.84 to 1.02), consistent with a small or no reduction in all-cause mortality over 3 to 7 years (Figure 4).

Effectiveness of Aspirin Chemoprevention in Patient Subgroups

The majority of 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 the elderly, women, and people 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 aged 70 to 84 years (RR, 0.49) as much as or more than it did for patients aged 60 to 69 years (RR, 0.46) and patients aged 50 to 59 years (RR, 0.58). In HOT, aspirin's effectiveness in patients over age 65 years (30% of the trial population) did not differ from its effect in those aged 50 to 64 years.[24] In TPT, however, patients aged 65 to 69 years did not benefit from aspirin (RR, 1.12) but younger patients did. Relative risks were 0.75 for patients aged 50 to 59 years and 0.61 for patients aged 60 to 64 years.

Table 3. Estimates of the role of aspirin in primary prevention of total fatal and nonfatal stroke

Trial	Aspirin events/ patients (%)	Control events/patients (%)	Odds ratio (95% CI)	Duration of therapy[a]	Annual risk for stroke among control patients	Approximate events avoided per 1,000 patients treated per year
BMD[5]	91/3,429 (2.65)	39/1,710 (2.28)	1.17 (0.80 to 1.71)	5.8 years	0.39%	0.6 excess events
PHS[4]	119/11,037 (1.08)	98/11,034 (0.89)	1.22 (0.93 to 1.59)	5.0 years	0.18%	0.4 excess events
TPT[7]	18/1,268 (1.42)	26/1,272 (2.04)	0.69 (0.38 to 1.27)	6.8 years	0.30%	0.9
HOT[8]	146/9,399 (1.55)	148/9,391 (1.58)	0.99 (0.78 to 1.24)	3.8 years	0.41%	0.1
PPP[9]	16/2,226 (0.72)	24/2,269 (1.06)	0.68 (0.36 to 1.28)	3.6 years	0.29%	0.9

[a]Values given are means except for the TPT value, which is the median.

Note: BMD indicates 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.

Table 4. Estimates of aspirin's role in hemorrhagic stroke and intracranial hemorrhage

Trial	Aspirin events/ patients (%)	Control events/patients (%)	Odds ratio (95% CI)	Duration of therapy	Annual risk approximate control group risk	Approximate excess bleeding events per 1,000 patients treated per year
BMD[5]	13/3,429 (0.38)	6/1,710 (0.35)	1.08 (0.41 to 2.85)	5.8 years	0.06%	0.05
PHS[4]	23/11,037 (0.21)	12/11,034 (0.11)	1.92 (0.95 to 3.86)	5.0 years	0.02%	0.2
TPT[7]	3/1,268 (0.24)	2/1,272 (0.16)	1.51 (0.25 to 9.03)	6.8 years	0.02%	0.12
HOT[8]	14/9,399 (0.15)	15/9,391 (0.16)	0.93 (0.45 to 1.93)	3.8 years	0.04%	0.03 fewer events
PPP[9]	2/2,226 (0.08)	3/2,269 (0.13)	0.67 (NR)	3.6 years	0.04%	0.12

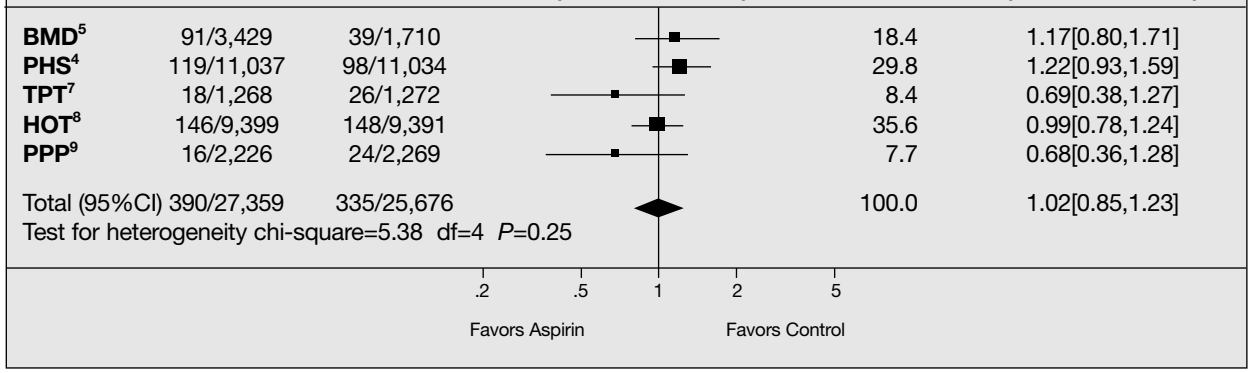
Note: BMD indicates British Male Doctors' Trial; CHD, coronary heart disease; HOT, Hypertension Optimal Treatment Trial; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial.

Sex

Only 2 of the 5 primary prevention trials included women (HOT and PPP). Kjeldsen et al[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 MIs in men (2.9/1,000 patient-years in the aspirin group vs 5/1,000 patient-years in controls; RR, 0.58; 95% CI, 0.41 to 0.81). However, its effect in women was smaller and not statistically significant (1.7/1,000 patient-years in the aspirin group vs 2.1/1,000 patient years in controls; RR, 0.81; 95% 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 in CHD reduction as men, but specific data were not presented.

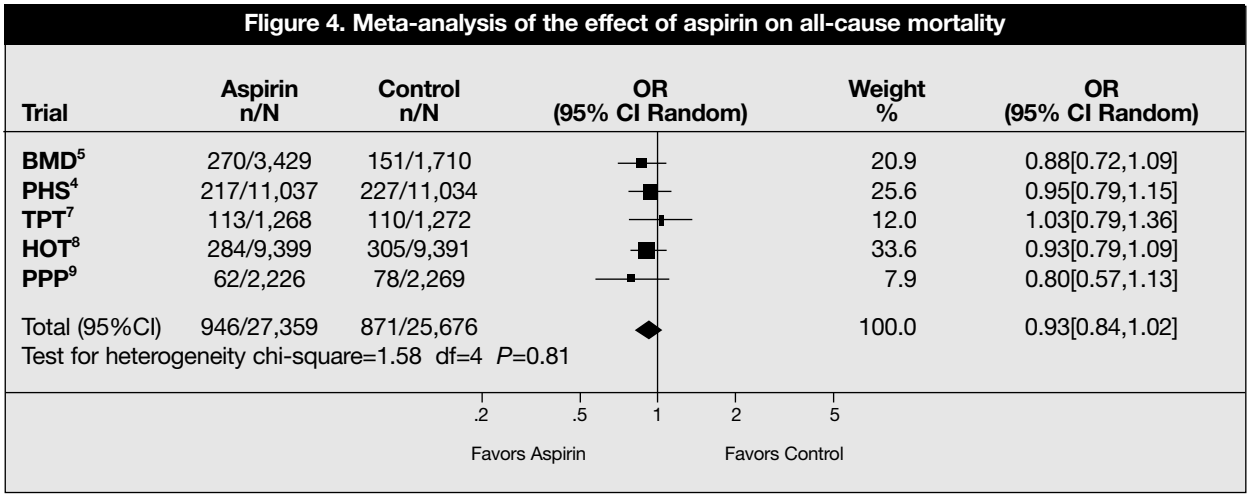
The question of whether sex modifies the effect of aspirin remains unclear. The Women's Health Study,

Figure 3. Meta-analysis of the effect of aspirin on fatal and nonfatal stroke events



Note: BMD indicates British Male Doctors' Trial; HOT, Hypertension Optimal Treatment Trial; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial. The result of the chi-square test for heterogeneity was 5.36 (P=0.25).

Figure 4. Meta-analysis of the effect of aspirin on all-cause mortality



Note: BMD indicates British Male Doctors' Trial; HOT, Hypertension Optimal Treatment Trial; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial. The result of the chi-square test for heterogeneity was 1.58 (P=0.81).

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 (RR, 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 CHD[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 et al[22] found that aspirin reduced total cardiovascular events in patients whose systolic blood pressure (SBP) was less than 130 mm Hg (RR, 0.59) but not in patients whose SBP was greater than 145 mm Hg (RR, 1.08). Patients with SBP between 130 and 145 mm Hg also had reduced risk (RR, 0.68). In PHS, patients who were taking aspirin and had SBP 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 SBP between 130 and 149 mm Hg and 0.52 for those with SBP between 110 and 129 mm Hg.[4] The HOT trial found significant reductions in CHD events among patients with treated hypertension, but did not have a comparison group without hypertension.[8]

Based on these data, aspirin seems to reduce CHD risk 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 CHD events was slightly larger (summary OR, 0.65; 95% 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 control participants in BMD, PHS and TPT, although these differences did not reach

statistical significance in any single trial (Table 4).[4,5,7] In the BMD trial, most strokes (over 60%) were of unknown cause because computed tomography scans were 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 et al[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 (95% CI, 0.88 to 2.1). Sudlow[25] recently performed a similar analysis using all 5 trials and reached a similar effect estimate (OR, 1.4; 95% CI, 0.9 to 2.0). In this analysis, the estimated annual excess risk with aspirin was 0.1 event per 1,000 users.

He et al[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 dose of aspirin was 273 mg daily, and the mean duration of treatment was 37 months. The summary relative risk for hemorrhagic stroke with aspirin use was 1.84 (95% CI, 1.24 to 2.74). He et al estimated that aspirin increased the absolute risk for hemorrhagic stroke by 12 events per 10,000 people (95% CI, 5 to 20 events) over approximately 3 years, or about 0.4 excess events per 1,000 users annually. This estimate is higher than that in Sudlow's meta-analysis, which included only primary prevention trials. He et al also concluded that the absolute risk of hemorrhagic stroke did not vary significantly according to preexisting CVD, mean age, sample size, dosage of aspirin, or study duration, although the statistical power to detect such differences was low due to the small number of total events.

Factors influencing the effect of aspirin on hemorrhagic stroke

Age. 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 colleagues' 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 aged 75 years or younger and 0.8% per year in patients older than 75 years.

Aspirin dose. The question of whether there is a "safe" dose of aspirin with respect to hemorrhagic stroke has been assessed 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 of hemorrhagic stroke. Reported use of low-dose aspirin (less than 1,225 mg weekly) was not associated with an increased risk of hemorrhagic stroke (OR, 1.00; 95% CI, 0.60 to 1.66) in multivariate risk-adjusted analyses. Larger amounts of aspirin were associated with hemorrhagic stroke (OR, 3.05; 95% 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 (OR, 1.7; 95% CI, 1.4 to 2.1) This translates to an excess risk for major, mostly gastrointestinal bleeding events of 0.7 (95% CI, 0.4 to 0.9) per 1,000 patients treated with aspirin per year.[25]

Several other systematic reviews have examined the risk for gastrointestinal bleeding with aspirin

Table 5. Estimates of the role of aspirin in gastrointestinal bleeding

Trial	Type of gastrointestinal bleeding	Cumulative incidence		*P* value	Excess bleeding events per 1,000 patients treated per year	Fatal gastrointestinal bleeding events	
		Aspirin group	Control group			Aspirin group	Control group
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[a]	1.7%	0.8%	NR	1.3	0	1
HOT[8]	Fatal and nonfatal major gastrointestinal bleeding[b]	0.8%	0.4%	NR	1.1	5	3
PPP[9]	Gastrointestinal bleeding[c]	0.8%	0.2%	NR	1.5	0	0

[a]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.

[b]Major bleeding was not found.

[c]Described as severe but nonfatal.

Note: BMD indicates 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.

use.[14-16,28] Roderick et al[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 doses exceeding 300 mg daily than in trials using lower doses, 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 and determined that ongoing use of aspirin would produce an excess of 2 major gastrointestinal bleeding events per 1,000 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 (greater than 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 OR, 1.68; 95% 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 1 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 (95% CI, 1.3 to 1.7).

Factors influencing the effect of aspirin on gastrointestinal bleeding

Aspirin Dose. 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 (OR, 1.015 per 100 mg change in dose; 95% CI, 0.984 to 1.047; *P*> 0.2). Cappelleri et al[17] performed a meta-analysis and meta-regression to determine the effect of dosage on the risk for gastrointestinal bleeding with

aspirin use among people 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 (eg, dyspepsia) increased with higher aspirin doses.

In a case-control study in Great Britain, Weil et al[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 (OR, 2.3 for 75 mg daily vs 3.9 for 300 mg daily). Kelly et al,[18] in another case-control study, found an estimated relative odds of 2.6 for dosages less than 325 mg daily and 5.8 for larger doses. The use of enteric-coated or buffered preparations did not appear to reduce risk. Concomitant use of other nonsteroidal anti-inflammatory agents or anticoagulants further increased risk.

Age. Silagy et al[21] examined the adverse effects of low-dose aspirin (100 mg daily) in a randomized, double-blind, placebo-controlled trial of 400 patients older than 70 years 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 found[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 the elderly.[26]

Gastrointestinal bleeding: summary. Aspirin chemoprevention, even at low doses, seems to increase the risk of gastrointestinal bleeding by a factor of 1.5 to 2. The absolute excess risk for major bleeding events appears to be approximately 3 per 1,000 middle-aged men receiving low-dose aspirin for more than 5 years. Higher rates (up to 2/1,000 people per year) are likely in elderly patients and perhaps among those using higher doses of aspirin.

Modeling 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 (aged 50 to 65 years) taking low-dose aspirin (162 mg or less per day).

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 CHD risk over 5 years. Table 7 shows the net impact of low-dose aspirin chemoprevention on

Table 6. Summary estimates of the effect of aspirin

Outcome	Odds ratio (95% CI)
Benefits	
Myocardial infarction	0.72 (0.60 to 0.87)
Coronary heart disease death	0.87 (0.70 to 1.09)
Total stroke	1.02 (0.85 to 1.23)
All-cause mortality	0.93 (0.84 to 1.02)
Harms	
Hemorrhagic stroke*	1.4 (0.9 to 2.0)
Major gastrointestinal bleed*	1.7 (1.4 to 2.1)

***Source:** Sudlow C. Antithrombotic treatment. *Clinical Evidence.* 5th ed. London: BMJ Publishing Group; 2001.

Table 7. Estimated benefits and harms of aspirin therapy for patients at different levels of risk for coronary heart disease events

	Estimated 5-year risk for CHD events at baseline		
Outcome	**1%**	**3%**	**5%**
Effect on all-cause mortality	No change	No change	No change
CHD events avoided, *n*	3 (1 to 4)	8 (4 to12)	14 (6 to 20)
Ischemic strokes avoided, *n*	0	0	0
Hemorrhagic strokes precipitated, *n*	1 (0 to 2)	1 (0 to 2)	1 (0 to 2)
Major gastrointestinal bleeding events precipitated, *n*	3 (2 to 4)	3 (2 to 4)	3 (2 to 4)

Note: Estimates based on 1,000 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 indicate 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 people, 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 people 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 to 7 years) are unknown. (6) Patients at high risk ((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.

patients with different levels of CHD risk. Treating patients with a moderately high risk of CHD events (5-year risk of 5%) would prevent 14 CHD events (range, 6 to 20). In low-risk patients, such as those with a 5-year CHD 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 1,000 people treated in each group, independent of CHD risk.

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 CVD but are at high risk for developing CHD in the next 5 years. Conversely, patients at low risk of CHD 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 CHD. 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 from our review in shared decision-making with patients requires an estimation of a given patient's absolute risk for CHD as well as his or her willingness to accept the risks of low-dose aspirin to avoid CHD events. Risk for future CHD 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 (LVH). 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/clincalc/heartrisk.html) or in printed form.[30] For tools that calculate only 10-year risk estimates, halving 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 CHD. 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 et al[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 et al[34] performed a meta-analysis of the first 4 primary prevention trials and reached similar estimates of the beneficial effects of aspirin. They chose to combine data on harms into a single category of "major bleeding events" induced and 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 CVD; this is equivalent to an event rate of 0.6% per year for CHD. Sanmuganathan et al concluded that aspirin was "safe and worthwhile" for people whose risk for CHD events exceeded 1.5% per year and was "unsafe" for people 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 et al[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 3 most recent trials. Outcomes were measured as changes in quality-adjusted life days. For 55-year-old patients, those at low risk (no risk factors in men; 0 or 1 risk factor in women) were harmed by aspirin therapy, whereas those at moderate to high risk (2 or more 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.

Based on 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 CHD risk. Consideration of underlying CHD risk, 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); for the adverse effects of aspirin: aspirin AND (gastrointestinal bleeding or cerebral hemorrhage). We supplemented our basic search strategies by examining bibliographies from other relevant articles, systematic reviews, and by seeking the advice of content experts.

Inclusion Criteria

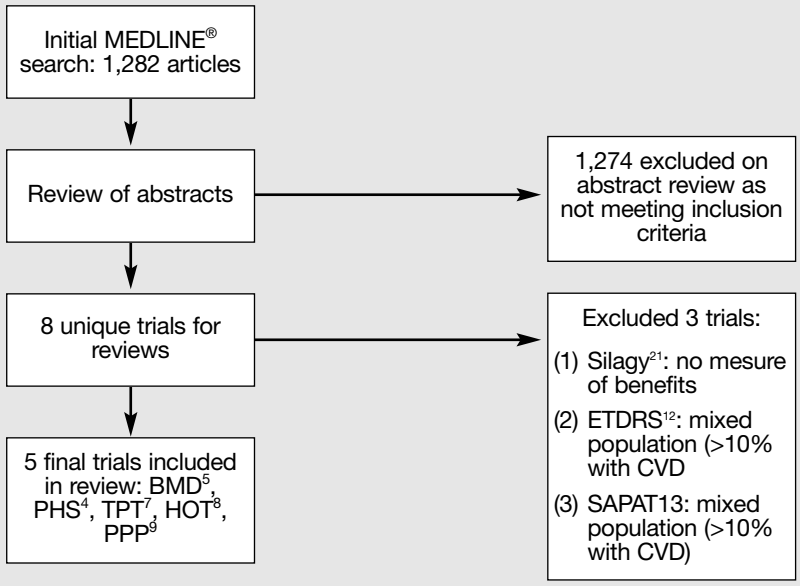
For studies examining the benefits of aspirin chemoprevention, we included randomized trials of at least 1 year's duration that met the following criteria: (1) compared aspirin with placebo or no aspirin; (2) included patients with no previous history of cardiovascular disease, including myocardial infarction,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

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.

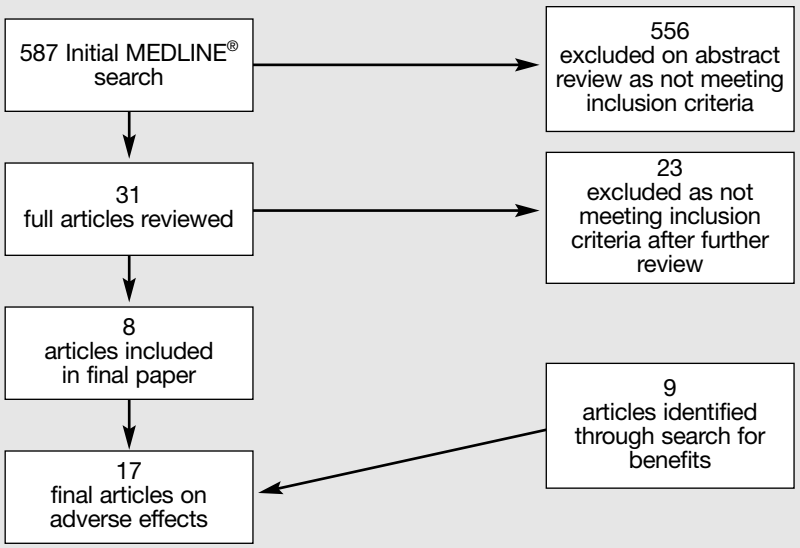
Data Extraction and Definition of Outcomes

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 CHD, including fatal acute myocardial infarction or death due to other ischemic heart disease; (2) fatal or nonfatal stroke; (3) total cardiovascular events (nonfatal acute myocardial infarction, death due to CHD, fatal or nonfatal stroke); and (4) all-cause mortality. Major harms examined were hemorrhagic stroke and major gastrointestinal bleeding.

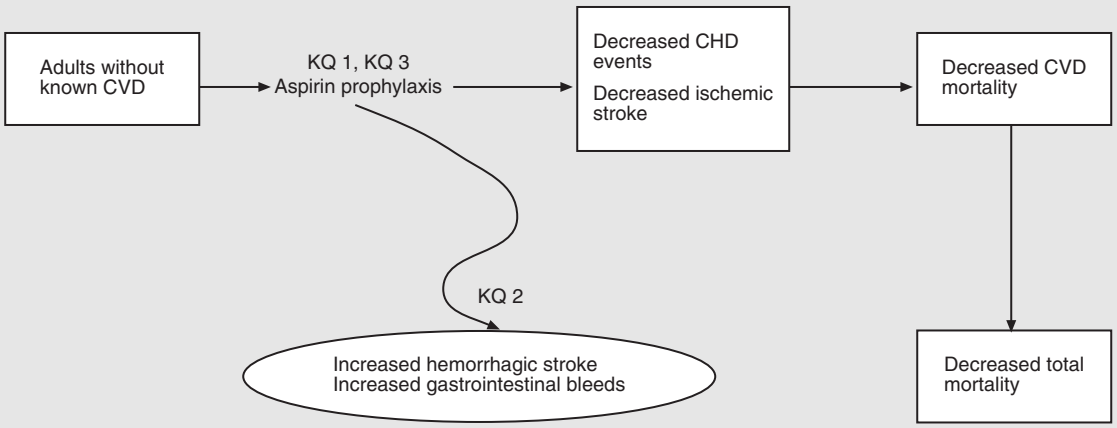
Search strategy—beneficial effects



Search strategy—harmful effects



Analytic framework: aspirin to prevent cardiovascular events



Note: KQ 1. Does aspirin chemoprevention in patients without known cardiovascular disease reduce the risk of mycardial infarction, stroke, and death? KQ 2. Does aspirin chemoprevention increase major gastrointestinal bleeding and/or hemorrhagic strokes? KQ 3. What is the balance of benefits and harms for aspirin therapy in patients with different levels of cardiovascular risk?

CHD indicates coronary heart disease; CVD, cardiovascular disease.

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