

## Summary of the Evidence

# Aspirin for the Primary Prevention of Cardiovascular Events

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## Abstract

**Background:** The use of aspirin to prevent cardiovascular disease (CVD) events in patients without a previous history of CVD is controversial.

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

**Data Sources:** MEDLINE® (1966 to May 2001).

**Study Selection:** We included (a) randomized trials of at least 1 year's duration that examined aspirin chemoprevention in patients without previously known CVD and (b) systematic reviews, recent trials, and observational studies that examined rates of hemorrhagic strokes and gastrointestinal bleeding secondary to aspirin use. Two investigators reviewed the abstract for each article to determine inclusion; disagreements were resolved by discussion among the entire review team after review of the full text.

**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:** When indicated, we performed meta-analysis using the DerSimonian and Laird random effects model. We then used the quantitative results of our review to model the consequences of treating patients with different levels of baseline coronary heart disease (CHD) risk. We identified five trials that examined the effect of aspirin on cardiovascular events in patients with no previous CVD. For patients similar to those enrolled in the trials, aspirin reduces the risk for the combined endpoint of nonfatal myocardial infarction and fatal coronary heart disease (CHD) by 28 percent (summary OR, 0.72; 95 percent CI, 0.60 to 0.87). Aspirin increased the risk of hemorrhagic strokes (summary OR, 1.4; 95 percent CI, 0.9 to 2.0) and major gastrointestinal bleeding (summary OR, 1.7; 95 percent CI, 1.4 to 2.1). All-cause mortality (summary OR, 0.93; 95 percent CI, 0.84 to 1.02) was not significantly affected over this time period.

For 1,000 patients with a 5 percent risk of CHD events over 5 years, aspirin would prevent 14 myocardial infarctions (range 6 to 20) but would cause 1 hemorrhagic stroke (range 0 to 2) and 3 major gastrointestinal bleeds (range 2 to 4). For patients with CHD risk of 1 percent over 5 years, aspirin would prevent 3 myocardial infarctions (range 1 to 4) but would cause 1 hemorrhagic stroke (range 0 to 2) and 5 major gastrointestinal bleeding events (range 2 to 4).

**Conclusions:** Aspirin can prevent myocardial infarctions but increases the risk of gastrointestinal bleeding and appears to increase the risk of hemorrhagic stroke. The net benefit of aspirin increases with increasing cardiovascular risk. The decision about whether to use aspirin chemoprevention requires consideration of the patient's cardiovascular risk as well as the patient's relative utility for the different clinical outcomes prevented or caused by its use.

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## Introduction

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.<sup>1</sup> 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.<sup>1</sup> The estimated direct and indirect costs of CHD and stroke were \$145 billion for 1999.<sup>2</sup>

Although the benefit of aspirin for patients with known CVD is well established,<sup>3</sup> 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.<sup>4,5</sup>

The results of these first two randomized, controlled trials were available to the members of the U.S. Preventive Services Task Force at the time of their 1996 recommendation.<sup>4,5</sup> 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.<sup>6</sup>

Two additional large primary prevention trials were published in 1998, and another was reported in January 2001.<sup>7,8,9</sup> 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 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 and/or hemorrhagic strokes?
3. What is the balance of benefits and harms for aspirin therapy in patients with different levels of CHD risk?

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## 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 percent confidence intervals (CIs).<sup>10</sup> 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).<sup>11</sup> 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, followup 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 percent 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.

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## Results

### Literature Searches

The results of our search strategy are shown in the [Appendix](#). We identified five 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).<sup>4,5,7-9</sup>

We excluded two large trials that examined the effect of aspirin on patients with diabetes or with stable angina because more than 10 percent of the participants had definite or suspected vascular disease.<sup>12,13</sup>

From our search for articles on adverse effects, we identified nine articles that examined the effect of aspirin on gastrointestinal bleeding and hemorrhagic stroke.<sup>3,14-21</sup>

### Studies Examining the Benefits of Aspirin Chemoprevention

#### Trial Characteristics

The characteristics of the five randomized trials, which included a total of more than 50,000 patients, are shown in [Table 1 \(Text Version\)](#). The duration of the trials ranged from 3 to 7 years. Only two trials (HOT and PPP) included women. Aspirin dose was 500 mg daily in BMD

and 162 mg or less per day in the other four trials. Most participants were middle-aged, although four of the five trials included substantial numbers of patients aged 70 to 80 years.

### Study Quality Assessment

Overall, the quality of the trials examining the effectiveness of aspirin was high. All five trials concealed allocation of randomization. Researchers and participants were blinded in three 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 percent of participants were lost to followup in BMD, PHS, and TPT, and 2.6 percent were lost to followup in HOT. In PPP, 7.7 percent of patients were lost to clinical followup, but data on vital status were obtained from census offices for 99.3 percent of the total sample.

During the BMD trial, 39 percent of participants in the aspirin group discontinued therapy, primarily because of dyspepsia; 11 percent of participants assigned to no therapy began taking aspirin during the course of the trial. In contrast, in the PHS trial, 14 percent of participants crossed over to the opposing treatment groups but rates of gastrointestinal discomfort did not differ significantly in each group. In PPP, 19 percent of patients assigned to aspirin discontinued it (8 percent due to side effects) and 7 percent 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 percent 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; [Table 2](#), [Text Version](#)). 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 percent CI 0.91, 3.71).<sup>4</sup>
- 18 events with aspirin versus 11 with placebo in the TPT trial (OR, 1.65; 95 percent CI, 0.78 to 3.51).<sup>22</sup>

Meta-analysis of the five trials for the combined outcome of confirmed nonfatal myocardial infarction or death from CHD produced a summary odds ratio of 0.72 (95 percent CI, 0.60 to 0.87) ([Figure 1](#), 6 KB; [Text Version](#)). 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 (Hansson L, Personal communication, 2000; Roncaglioni C, Personal communication, 2001). Of the five trials, only PHS reported a statistically significant decrease in risk with aspirin (OR, 0.64; 95 percent CI, 0.42 to 0.99). Cumulative CHD mortality rates in the placebo group were

low, ranging from 0.15 percent in HOT to 2.7 percent in BMD and TPT. Meta-analysis of the five trials found a summary odds ratio of 0.87 (95 percent CI, 0.70 to 1.09) ([Figure 2](#), 6 KB; [Text Version](#)). 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 total incidence of stroke depends on the patient's underlying risk for each stroke subtype.<sup>23</sup>

Overall stroke rates were lower than expected (based on age and risk factors) in all five primary prevention trials ([Table 3](#), [Text Version](#)). In each trial, control participants who had not been given aspirin had a less than 2 percent 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.<sup>7,23</sup> 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.<sup>4,5</sup> The summary estimate ([Figure 3](#), 6 KB; [Text Version](#)) showed no difference in total stroke overall (OR, 1.02; 95 percent 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,<sup>8</sup> and BMD did not use neuroimaging to differentiate ischemic from hemorrhagic strokes.<sup>5</sup> The PHS trial reported 91 ischemic strokes with aspirin and 82 with placebo (OR, 1.11; 95 percent CI, 0.83 to 1.50).<sup>5</sup> In TPT, 10 ischemic strokes occurred in the aspirin group and 18 occurred in the placebo group (OR, 0.55; 95 percent CI, 0.25 to 1.20).<sup>7</sup> The PPP trial had 14 ischemic strokes in the intervention group and 21 in the "no aspirin" group.<sup>9</sup>

Despite the uncertainty of stroke classification, Hart et al.<sup>19</sup> combined data from the first four primary prevention trials <sup>4,5,7,8</sup> and concluded that aspirin appeared to have no effect on ischemic strokes in the middle-aged, relatively low-risk patients (RR, 1.03; 95 percent CI, 0.87 to 1.21).<sup>19</sup>

### All-Cause Mortality

None of the five 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 percent to 10 percent. The summary odds ratio for the effect of aspirin on all-cause mortality was 0.93 (95 percent CI, 0.84 to 1.02), consistent with a small or no reduction in all-cause mortality over 3 to 7 years ([Figure 4](#), 6 KB; [Text Version](#)).

### Effectiveness of Aspirin Chemoprevention in Patient Subgroups

The majority of participants in the five 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 percent of the trial population) did not differ from its effect in those aged 50 to 64 years. 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.

**Sex.** Only two of the five primary prevention trials included women (HOT and PPP). Kjeldsen et al. 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 percent 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 percent 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, a primary prevention trial that will test low-dose aspirin in approximately 40,000 patients, is expected to clarify risks and benefits among women.<sup>10</sup>

**Patients with Diabetes Mellitus.** The proportion of patients with diabetes mellitus was small in each trial (PPP, 17 percent; HOT, 8 percent; PHS, 2 percent; BMD, 2 percent; TPT, 2 percent). 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<sup>23</sup> and a single trial in diabetic patients with and without CHD<sup>12</sup> 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.<sup>22</sup> 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.<sup>4</sup> The HOT trial found significant reductions in CHD events among patients with treated hypertension, but did not have a comparison group without hypertension.<sup>8</sup>

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 three trials we rated as good (PHS, TPT, HOT). The reduction in total CHD events was slightly larger (summary OR, 0.65; 95 percent 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](#), [Text Version](#)).<sup>4,5,7</sup> In the BMD trial, most strokes (over 60 percent) were of unknown cause because computed tomography scans were not performed in most cases.<sup>5</sup> In HOT and PPP, hemorrhagic strokes were almost equally common in the intervention and control groups.<sup>8,9</sup>

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.<sup>19</sup> pooled the results of the first four primary prevention studies and estimated that the relative risk for hemorrhagic stroke due to long-term aspirin use was 1.36 (95 percent CI, 0.88 to 2.1). Sudlow<sup>24</sup> recently performed a similar analysis using all five trials and reached a similar effect estimate (OR, 1.4; 95 percent 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.<sup>3</sup> 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 percent 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 percent 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 percent 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,<sup>25</sup> 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 percent per year in patients aged 75 years or younger and 0.8 percent 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<sup>26</sup> 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 percent CI, 0.60 to 1.66) in multivariate risk-adjusted analyses. Larger amounts of aspirin were associated with hemorrhagic stroke (OR, 3.05; 95 percent CI, 1.02 to 9.14).

### Gastrointestinal Bleeding

Aspirin increased the rates of gastrointestinal bleeding in all five 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](#), [Text Version](#)).

Pooling the data on major extracranial bleeding from the five primary prevention trials, Sudlow estimated that aspirin increased the risk for major extracranial bleeding (OR, 1.7; 95 percent CI, 1.4 to 2.1) This translates to an excess risk for major, mostly gastrointestinal bleeding events of 0.7 (95 percent CI, 0.4 to 0.9) per 1,000 patients treated with aspirin per year.<sup>24</sup>

Several other systematic reviews have examined the risk for gastrointestinal bleeding with aspirin use.<sup>14-16,27</sup> Roderick et al.<sup>15</sup> 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<sup>14</sup> 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<sup>27</sup> 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 percent CI, 1.51 to 1.88). The absolute risk difference was 1.05 percent. 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 nine trials of low-dose aspirin prevention that had lasted at least 3 months;<sup>16</sup> the pooled odds ratio for all gastrointestinal bleeding was 1.5 (95 percent CI, 1.3 to 1.7).

### Factors Influencing the Effect of Aspirin on Gastrointestinal Bleeding

**Aspirin Dose.** Derry and Loke<sup>27</sup> 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 percent CI, 0.984 to 1.047;  $P > 0.2$ ). Cappelleri et al.<sup>17</sup> 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 (e.g., dyspepsia) increased with higher aspirin doses.

In a case-control study in Great Britain, Weil et al.<sup>20</sup> 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.,<sup>18</sup> 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.<sup>21</sup> 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 pre-existing vascular disease. The reported absolute rate of any gastrointestinal bleeding in the aspirin group was 3 percent 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<sup>3</sup> or have not examined<sup>27</sup> 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.<sup>25</sup>

### **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 \(Text Version\)](#) 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 five 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 \(Text Version\)](#) shows the net impact of low-dose aspirin chemoprevention on patients with different levels of CHD risk. Treating patients with a moderately high risk of CHD events (5-year risk of 5 percent) would prevent 14 CHD events (range, 6 to 20). In low-risk patients, such as those with a 5-year CHD risk of 1 percent, 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.

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