Evaluation of the Benefits and Risks of Low-Dose Aspirin in the Secondary Prevention of Cardiovascular and Cerebrovascular Events

Steven M. Weisman, PhD; David Y. Graham, MD

Background: In spite of the clear evidence of benefit of aspirin in the secondary prevention of cerebrovascular and cardiovascular thrombotic events, its use in patients at high risk due to a previous event remains suboptimal. A possible explanation for this underuse is concern regarding the relative benefit in relation to the potential risk for serious gastrointestinal events.

Objective: To compare the benefit and gastrointestinal risk of aspirin use for the secondary prevention of thromboembolic events.

Design: A meta-analysis was conducted using 6 trials (6300 patients) meeting the inclusion requirement of use of low-dose aspirin (≤325 mg/d) in approved secondary prevention indications.

Results: Aspirin reduced all-cause mortality by 18%. In addition, aspirin use reduced the number of strokes by 20%, myocardial infarctions by 30%, and other “vascular events” by 30%. Alternately, patients who took aspirin were 2.5 times more likely than those in the placebo group to have gastrointestinal tract bleeding. The number needed to treat for aspirin to prevent 1 death from any cause of mortality was 67, while 100 needed to be treated to detect 1 nonfatal gastrointestinal tract bleeding.

Conclusion: Aspirin use for the secondary prevention of thromboembolic events has a favorable benefit-to-risk profile and should be encouraged in those at high risk.

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SINCE ITS introduction in 1899, aspirin has been recognized as a drug with a favorable benefit-to-risk ratio. Ironically, aspirin was advertised in the 1920s with the claim that it did not affect the heart, unlike other drugs of the time, which were thought to have an “enfeebling” effect. More than 100 years after its introduction, it is now clear that aspirin can positively affect the heart, especially in the management of acute evolving myocardial infarction. Data from numerous controlled clinical trials provided the basis for its approval by the US Food and Drug Administration (FDA) for use in prevention of thromboembolic events in individuals who had a previous myocardial infarction, transient ischemic attack (TIA), or stroke. In spite of the clear evidence of benefit of aspirin in the secondary prevention of vascular events, its use in patients at high risk due to a previous event remains suboptimal.1 One possible explanation for underuse of aspirin by physicians is concern regarding the potential for serious adverse effects on the gastrointestinal tract (GI).

Cardiovascular disease, which includes myocardial infarction, stroke, and peripheral vascular diseases, is a leading cause of death in the United States and other major developed countries, accounting for more than 900,000 deaths annually in the United States alone.2 Long-term aspirin administration has been shown to confer a benefit on risk of subsequent myocardial infarction, stroke, and vascular death among patients with underlying cardiovascular disease, primarily by inhibiting platelet aggregation. The 1994 Antiplatelet Trialists’ Collaboration3 overview analysis of randomized trials of antiplatelet therapy involving more than 54,000 high-risk patients with prior evidence of cardiovascular disease demonstrated that 40 events could be avoided per 1000 patients with prior myocardial infarction, stroke, or TIA when treated with aspirin for 2 to 3 years. Furthermore, these results provided no evidence that higher doses (500-1500 mg) were more effective than lower doses (≤325 mg). Based on these and other findings, the American College of Cardiology and the American Heart Association4 recommended that daily aspirin therapy at a dose of at least 75 to 325

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mg be considered for all patients at elevated risk of subsequent events due to a history of vascular disease.

Today, aspirin is widely used as a thromboprophylactic agent, with tens of millions of tablets consumed each day. As millions of individuals use aspirin for the secondary prevention of cardiovascular and cerebrovascular events, our goal was to compare benefits of treatment with the potential risk of GI injury under conditions of appropriate use. Earlier analyses have included patient populations at various levels of risk (ie, those in primary and secondary prevention trials), as well as aspirin at doses higher than currently recommended. As a result, these analyses may have either underrepresented the benefit or exaggerated the risk. This overview analysis focuses only on the FDA-approved uses of low-dose aspirin (50-325 mg/d) in the secondary prevention of myocardial infarction and stroke, with the aim of providing additional insight to physicians and patients regarding the benefits and risks of aspirin use in this high-risk population.

### METHODS

A review of the computerized literature databases MEDLINE, EMBASE, and Excerpta Medica was performed to identify all published reports after 1970 of aspirin use for FDA-approved secondary prevention indications, as summarized in the FDA’s 1998 rule and updated professional labeling for aspirin. The approved indications include stroke in those who had a previous event or a TIA and myocardial infarction in those who had a previous myocardial infarction or have a history of angina. In addition, reference lists of published secondary prevention trials and overviews were examined for additional sources. Studies included in this review were limited to randomized, placebo-controlled interventions with an aspirin-only arm, with low-dose aspirin defined as daily doses of 50 to 325 mg. Furthermore, reports were required to provide both efficacy and safety end points. Trials were excluded if aspirin was (1) administered for less than 3 months; (2) prescribed short term for thromboprophylaxis in procedures such as angioplasty or coronary artery bypass grafts; (3) used for nonprevention indications, such as pain, headache, or arthritis; (4) coadministered with another agent; or (5) used to prevent cardiovascular events in otherwise healthy individuals (primary prevention).

Data from each published study were abstracted by a third for quality control. Data related to inclusion and exclusion criteria, health status on entry, and outcomes were collected on specially developed forms and entered into corresponding Microsoft Excel (Microsoft Corp, Redmond, Wash) data cells that were checked against hard copy entries. As the objective of this analysis was to evaluate aspirin alone, treatment arms involving other antithrombotic therapies or aspirin in combination with other agents were not abstracted.

Consistent with the desire to assess both benefit and risk, detailed information was collected on all fatal and nonfatal vascular events from all randomized subjects. Outcome data consisted of myocardial infarction, stroke, vascular death, vascular event (ie, any stroke, myocardial infarction, or other vascular events defined as possibly or definitely of cardiac, cerebral, embolic, hemorrhagic, or unknown cause), and all-cause mortality. In addition, we collected data on serious adverse events related to bleeding. We focused our review on GI bleeding, a common and expected adverse effect of aspirin therapy. Bleeding events were abstracted regardless of their severity. Subjective tolerability was not evaluated because the collection of such events across the trials was not consistent.

We included all studies for the secondary prevention of cardiovascular or cerebrovascular disease meeting the above-mentioned criteria regardless of precipitating event. Each of these studies varied in the outcome data collected, duration of treatment, and length of follow-up. Because outcome data were reported differently across the studies, results for categories were pooled only if they were reported the same way. To facilitate comparison across studies with differing end points, the summary measure “vascular events,” defined as myocardial infarction, stroke, or other vascular event (including vascular death), was used. Individual outcome variables (eg, myocardial infarction, stroke, and death) are presented for the trials providing data with respect to these outcomes (Table 1). While follow-up times varied across studies, placebo and aspirin arms within each study had the same follow-up time.

Relative risks were estimated using standard statistical approaches. The data were transferred to SPSS version 10 (SPSS Inc, Chicago, Ill) for sorting, listing, and production of descriptive statistics. Risk test for homogeneity of results across all studies with reported outcomes, and estimates of the common risk ratio were calculated using the exact method, performed with StatXact4 (Cytel Software Corp, Cambridge, Mass).

Because of differences in the length of follow-up across the studies, we could not use the Peto fixed-effects model to calculate a pooled odds ratio. Instead, we computed the relative risk for each outcome assuming a constant follow-up time for each study. Absolute risk reductions and 95% confidence intervals (CIs) were also calculated for each outcome variable. Absolute risk reductions were not aggregated because of differences in follow-up periods across studies. As such, they are only presented descriptively. The common risk and 95% CI were calculated using all studies with reported outcomes. Homogeneity of risk across studies was calculated using the method of Breslow and Day. The numbers needed to treat (NNT) for GI bleeding events and all-cause mortality were calculated by using the pooled risk ratio and the pooled placebo event rates.

### RESULTS

The literature review through March 31, 2000, resulted in the identification of 6 trials, which contributed 6300 patients to the analysis: 3127 to aspirin alone and 3173 to placebo (Table 2). Of these 6300 patients, 2427 evaluated patients experienced a previous myocardial infarction, and 1757 had a history of TIA or stroke. Among these patients, there were 558 subsequent myocardial infarctions, 424 strokes (265 thrombotic, 24 hemorrhagic, and 135 undefined), and 91 other vascular events. There were 532 deaths and 58 reports of GI bleeding of any severity. Cases were included regardless of whether they required hospitalization or surgery. There were no cases of GI bleeding that were fatal. Studies contributed to the analysis of

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Subjects</th>
<th>Studies Reporting Outcome, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular events*</td>
<td></td>
<td></td>
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<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
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<tr>
<td>Stroke</td>
<td></td>
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<tr>
<td>Gastrointestinal tract bleeding</td>
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<tr>
<td>Randomized subjects</td>
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</tbody>
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*Myocardial infarction, stroke, and other vascular events, including vascular death (calculated).

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a specific outcome only when at least 1 occurrence of that outcome was reported. Studies varied in both the definition and number of outcomes reported. Many used aggregate end points that included combinations of stroke, myocardial infarction, and vascular death.

As depicted in Table 3, all 6 studies reported total mortality. Myocardial infarction and GI bleeding were reported in 5 of the 6 studies, while stroke was reported in only 2 studies. To include all studies, we created the event category “vascular events” to summarize all reports of myocardial infarction, stroke, and other vascular events including vascular death. Because vascular death was not reported consistently across studies, we used the more conservative all-cause mortality to assess the effects of aspirin on mortality.

Relative risk estimates for all-cause mortality are also summarized in Table 3. In the aspirin and placebo groups, there were 241 and 291 deaths, respectively. Relative risk calculations for each of the individual studies ranged from 0.5 (95% CI, 0.2-1.1; \( P = .08 \)) to 1.0 (95% CI, 0.3-3.0; \( P > .99 \)), suggesting that numbers were too small in individual studies to determine with confidence whether there is an impact on all-cause mortality, in spite of directional support. The findings of our analysis demonstrate that the results are homogeneous across the studies (test for homogeneity, \( P = .7 \)), allowing the calculation of common risk ratio of 0.82 (95% CI, 0.7-0.99; \( P = .03 \)) for aggregation of these studies. Thus, the data suggest that aspirin reduces the risk of death by approximately 20% in the studied population. Absolute risk reductions ranged from 0.9%±3.7% (52-month follow-up) to 18.6%±7.7% (3-month follow-up).

These findings suggest the conclusion that the reduction in the risk of death attributed to aspirin use is accompanied by similar degrees of risk reduction in myocardial infarction (30%) and vascular events (30%). Because the stroke findings involved only 2 studies, the results are suggestive of a benefit of aspirin, but are not sufficiently conclusive.

The risk of GI bleeding, the most common serious adverse event associated with extended aspirin use, was similarly evaluated (Table 5). Five of the 6 studies meeting the inclusion criteria reported GI bleeding.\(^{10-14}\) Because adequate information on the severity of this variable was lacking, we included any report of GI bleeding in our analyses. In spite of this conservative approach, GI bleeding was a rare finding, with only 58 reports across the 6 studies (41 in the aspirin groups; 17 in the placebo groups). Only about half of the cases of GI bleeding were deemed severe enough to require withdrawal. Importantly, there were no reported deaths related to GI bleeding (Table 6), and GI bleeding led to almost no permanent morbidity (that was reported by the investigators). Only 1 report, the United Kingdom Transient Ischaemic Attack (UK-TIA) trial,\(^{10}\) demonstrated a statisti-
Aspirin remains one of the most widely used and consequently most studied therapies in the history of medicine. It is used at high doses to alleviate the pain and inflammation of arthritis, at moderate doses for short-term management of acute pain, and at low doses for cardiovascular and cerebrovascular disease prevention. Within the vascular disease management arena, aspirin is indicated for use in a variety of patient risk strata.

Recently, there has been significant discussion over the relative benefits and risks of aspirin therapy in the prevention of cardiovascular and cerebrovascular events. While it is widely accepted that aspirin is beneficial, there is controversy with respect to which patients receive the greatest benefit with the least risk. It is likely that confusion over the relative benefits and risks of treatment has been in part responsible for underuse of this highly effective, inexpensive therapy among the large group of patients at risk for cardiovascular disease. Misunderstanding of the benefits of aspirin may result from the diverse nature of the conditions for which aspirin is indicated, as well as the attribution of risk from various conditions in which the dose, formulation, or the benefit-risk relationship may differ. For instance, in the long-term management of inflammatory conditions in which high-dose aspirin is used, a greater frequency of adverse effects would be expected than would be observed in the short-term management of acute pain. Therefore, the suggestion that an individual would experience the same potential for an adverse event whether treating acute pain as using it in the long-term management of arthritis would not be appropriate. Likewise, in patients at high risk of cardiovascular events, the absolute benefit would be expected to be greater than that of lower-risk patients, while the rate of adverse GI events might be expected to remain constant. As such, the benefit-to-risk relationship can vary tremendously and can only be intelligently discussed in the context of intended use.

The adverse effects of aspirin have been well studied and characterized. Gastrointestinal tract perforation, ulceration, and bleeding are expected adverse effects associated with long-term aspirin therapy. Because inhibition of prostaglandin synthesis is the common mechanism for both the beneficial thromboprophylactic effects and the adverse effects on the GI tract, it is unlikely that the benefits can be achieved without some degree of risk. A number of studies have examined the relationship between aspirin dose and toxic effects with conflicting results. Cameron demonstrated an exponential increase in the relative risk of developing a chronic gastric ulcer relative to the number of aspirin tablets consumed per week. In

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**Table 5. Gastrointestinal Tract Bleeding**

<table>
<thead>
<tr>
<th>Source</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elwood et al.†, 1974</td>
<td>300/0</td>
<td>615/634</td>
</tr>
<tr>
<td>Lewis. 1985</td>
<td>32/4</td>
<td>625/641</td>
</tr>
<tr>
<td>The RISC Group, 11 1990</td>
<td>75/0</td>
<td>189/199</td>
</tr>
<tr>
<td>Zaijia et al., 1991</td>
<td>50/0</td>
<td>216/211</td>
</tr>
<tr>
<td>The SALT Collaborative Group, 1991</td>
<td>75/0</td>
<td>676/684</td>
</tr>
<tr>
<td>Farrell et al., 1991</td>
<td>300/0</td>
<td>806/814</td>
</tr>
</tbody>
</table>

*Common risk ratio, 2.5 (95% confidence interval, 1.4-4.7; P = .001); test for homogeneity, P = .05. NR indicates not reported.
†Data are for aspirin/control groups.

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**Table 6. Number of Severe Gastrointestinal Tract Bleeding Events**

<table>
<thead>
<tr>
<th>Source</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elwood et al.†, 1974</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lewis, 1985</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>The RISC Group, 11 1990</td>
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<td>4</td>
</tr>
<tr>
<td>Zaijia et al., 1991</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>The SALT Collaborative Group, 1991</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

*Severe or causing discontinuation of study drug. There were no deaths.

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Son was made by calculating the NNT with aspirin to either prevent 1 death or cause 1 GI bleeding event. All-cause mortality occurred in 9.2% of the placebo group and 7.7% of the aspirin group. Conversely, 1.6% of the aspirin group had a GI hemorrhage compared with 0.6% in the control group. Based on the differences between the rates of the aspirin- and placebo-treated patients, we determined that 1.5 deaths could be prevented for every nonfatal GI bleeding attributed to the use of aspirin.
patients taking 10 or fewer tablets per week, the relative risk was 1 or less; at 40 tablets per week, the relative risk was nearly 6.0. Two trials have directly compared different doses of aspirin.\textsuperscript{10,17} The UK-TIA study,\textsuperscript{10} found that patients randomized to 1200 mg/d were more likely to experience subjective GI symptoms, as well as hemorrhage, than patients who were randomized to 300 mg/d. Likewise, the Dutch TIA Trial Study Group\textsuperscript{17} found that patients randomized to 30 mg/d had a modest reduction in serious bleeding and GI symptoms compared with patients randomized to 283 mg/d. Results from meta-analyses, including that of the Antiplatelet Trialists’ Collaboration,\textsuperscript{3} support the benefits of low doses of aspirin. In contrast to these findings, a recent meta-analysis published in the British Medical Journal\textsuperscript{3} suggests that lower doses may not enhance the benefit-to-risk relationship. However, this conclusion, as well as that of previous analyses, is confounded by the inclusion of low-risk individuals without underlying cardiovascular disease. Inclusion of such patients may distort the benefit-to-risk ratio because the absolute benefit in many of these patients would be expected to be significantly less than that observed in secondary prevention studies.

Given the previous evidence of equal antithrombotic effectiveness of high, medium, and low doses of aspirin\textsuperscript{3} and the possibility that the lower doses increasingly being used might enhance GI safety, we sought to carefully evaluate the benefit-to-risk relationship of low-dose aspirin therapy in the secondary prevention of myocardial infarction and stroke. The purpose of our evaluation was to provide insight regarding the relative benefits and risks of aspirin treatment in the currently FDA-approved uses of aspirin as described in Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use: Final Rule for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination with Antacid Drug Products.\textsuperscript{6} As the dose-response relationship for adverse events could be an important clinical determinant of risk, we restricted our evaluation to currently approved doses for the above-mentioned indications. As such, our analysis focused on the long-term use of low-dose aspirin at dosages less than or equal to 325 mg/d (1 regular-strength tablet) for the prevention of cardiovascular events in patients who have previously experienced a myocardial infarction (or unstable angina), TIA, or stroke. This restriction resulted in the exclusion of many of the early secondary prevention trials that used dosages in excess of 325 mg/d.

Our findings confirm the benefits of low-dose aspirin therapy (≤325 mg) in high-risk patients seen previously. Our overview analysis of the 6 randomized, placebo-controlled, secondary prevention studies, in contrast to other meta-analyses that included broader indications and risk strata, demonstrate an 18% reduction in the risk of death. While each of the 6 studies on its own showed a directional trend toward reducing the risk of death, no single study achieved statistical significance. When evaluated together, these studies demonstrate a statistically significant reduction in all-cause mortality, a finding that has not been previously described for aspirin. Previous findings of a mortality benefit have been restricted to vascular death. The finding of a statistically significant benefit in reducing all-cause mortality is a powerful indicator of the life-saving properties of aspirin, since all-cause mortality is the ultimate end point for establishing effectiveness.

The benefits observed in preventing fatal outcomes were evaluated in conjunction with the potential for serious GI adverse effects. We confirmed findings by other groups\textsuperscript{1,3} that long-term aspirin intake significantly increases the risk of GI bleeding. Our analysis demonstrates a 2.5-fold increase in the risk of such an event. Nonetheless, the number of events were few, with only 58 nonfatal cases reported out of 6300 patients evaluated for a minimum of 3 months. In all cases, the GI adverse event was managed effectively, with no reports of death.

Our analysis included all GI bleeding events and not only those that were serious or major. It does not, however, address occult GI blood loss, which may be of concern to practicing physicians, since it would not be reported as a bleeding “event.” While numerous studies have indicated that low doses of aspirin might increase occult blood loss,\textsuperscript{18,20} prior studies showed that the amount was trivial and dose related.\textsuperscript{21} To our knowledge, the clinical significance of aspirin-induced GI microbleeding with low-dose aspirin use has never been demonstrated.

There are data suggesting an adverse interaction between nonsteroidal anti-inflammatory drugs, including aspirin, and Helicobacter pylori infection.\textsuperscript{22} For example, a recent placebo-controlled, double-blind, randomized trial prospectively assessed the effect of \textit{H pylori} on gastric mucosal injury in subjects receiving low-dose aspirin treatment and reported significantly more gastric mucosal injury in patients using aspirin.\textsuperscript{23} Two other studies\textsuperscript{24,25} also suggest that \textit{H pylori} infection may increase the risk of clinical GI events including bleeding. Thus, eradication of \textit{H pylori} infection may be one method of reducing the risk of GI bleeding associated with aspirin use.\textsuperscript{26} This notion is supported by a study by Chan et al,\textsuperscript{27} who reported that eradication of \textit{H pylori} infection reduced rebleeding rates in patients requiring low-dose aspirin therapy who had previously bled. While further studies are needed, the available data suggest that the already favorable risk-benefit ratio associated with the use of aspirin for prevention of cardiovascular events may be able to be improved.

To place the benefits and risks in better perspective, we calculated the NNTs to prevent 1 death as well as to cause 1 GI bleeding event. We determined that for every 67 patients treated to protect a subsequent myocardial infarction or stroke, 1 life could be saved with low-dose aspirin therapy. This compares favorably with NNTs required to prevent a death with the use of anticoagulants, β-blockers, and angiotensin-converting enzyme inhibitors in the secondary prevention of ischemic heart disease.\textsuperscript{28} In our evaluation, we found that 100 is the number of patients needed to be treated to cause a GI bleeding event. These findings suggest, ignoring \textit{H pylori} and other potential risk factors, that 1.5 lives can be saved for every GI bleeding event attributed to aspirin use. Our results do not differ appreciably from those of the SALT investigators,\textsuperscript{12} who found the NNT with aspirin to prevent recurrent stroke to be 106 patients. Using results from a meta-analysis including aspirin use for both pri-
mary and secondary prevention, Derry and Locke\(^4\) conclude that 2 recurrent strokes could be prevented for every 1 GI hemorrhage caused, a finding virtually identical to ours.

While GI bleeding was increased with the use of aspirin in the secondary prevention studies evaluated, this outcome was rare, manageable, and led to no deaths. Furthermore, the potential for this adverse outcome must be compared with the highly significant and clinically meaningful finding of a reduction in all-cause mortality, the gold standard for drug effectiveness. This benefit, coupled with substantial and comparable reductions in nonfatal vascular events, leads to the conclusion that the benefit-to-risk ratio for aspirin in the secondary prevention of cardiovascular and cerebrovascular events is highly favorable.

While our analyses were restricted to the secondary prevention database, there is significant evidence that the benefits of aspirin treatment accrue to “at-risk” populations who have not had a previous thrombotic event. The National Cholesterol Education Program\(^2\) recommends that patients with an absolute 10-year risk of 20% or higher for developing heart disease should be candidates for drug and dietary intervention regardless of the occurrence of a previous event. Such an event rate is not uncommon in individuals with multiple risk factors in which the risk of developing heart disease is often equal to or higher than observed in many patients who have had a previous event, but without additional risk factors. Patients with an estimated 10-year risk between 10% and 20% may also benefit from drug and dietary therapy. It is likely that the use of aspirin in these patients would be associated with a positive benefit-to-risk relationship similar to that demonstrated using the secondary prevention database. The overview analyses conducted by Sanmuganathan and colleagues\(^3\) demonstrated a threshold coronary event risk for the appropriate use of aspirin in primary prevention to be equal or greater than 1.0% to 1.5% per year.

These findings should assist physicians and patients in understanding the role and safety profile of aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Our overview analysis, coupled with the sheer number of people worldwide who take this medication without incident and the extensive historical and current evidence, clearly support broader use of aspirin.

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