Risk of Hemorrhagic Stroke With Aspirin Use
An Update

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Background—Low-dose aspirin is an important therapeutic option in the secondary prevention of myocardial infarction (MI) and ischemic stroke, especially in light of its unique cost-effectiveness and widespread availability. In addition, based on the results of a number of large studies, aspirin is also widely used in the primary prevention of MI. This review provides an update of the available data to offer greater clarity regarding the risks of aspirin with respect to hemorrhagic stroke, as well as insights regarding patient selection to minimize the risk of this complication.

Summary of Review—In the secondary prevention of cardiovascular, cerebrovascular, and ischemic events, the evidence supports that the benefits of aspirin treatment significantly outweigh the risk of a major hemorrhage. The evidence from primary prevention of MI studies, including that from the recent Women’s Health Study evaluation of aspirin use in healthy women, demonstrate that the increased risk for hemorrhagic stroke is small, is comparable to the secondary prevention studies, and fails to achieve statistical significance. A reasonable estimate of the risk of hemorrhagic stroke associated with the use of aspirin in primary prevention patients is 0.2 events per 1000 patient-years, which is comparable to estimates of the risk associated with the use of aspirin in secondary prevention patients.

Conclusions—When considering whether aspirin is appropriate, the absolute therapeutic cardiovascular benefits of aspirin must be balanced with the possible risks associated with its use, with the most serious being hemorrhagic stroke. (Stroke. 2005;36:1801-1807.)

Key Words: aspirin ■ intracerebral hemorrhage ■ primary prevention ■ stroke, hemorrhagic

Despite >100 years of use, acetyl salicylic acid (aspirin) has only been recognized for the prevention of myocardial infarction (MI) and ischemic stroke for the past 25 years. Over this period, based on its unique cost-effectiveness and widespread availability, the utilization of aspirin has expanded substantially for both primary and secondary prevention of cardiovascular events, providing significant insight into its safety and effectiveness.

The decision as to which patients to treat must weigh the benefits of chronic aspirin therapy against the possible risks associated with its use, including the risk of intracerebral and subarachnoid hemorrhage, the most serious risks associated with the use of aspirin.1–7 Although a number of published primary and secondary prevention studies have suggested a small increased risk of such events with aspirin, the absolute numbers of cases is exceedingly small, leading to wide confidence intervals around the risk estimates. The uncertainty is further enhanced by diagnostic inaccuracy, definitional inconsistencies, and few study participants with stroke actually having computed tomography scanning to detect potential contributing underlying diseases or complications. In addition, there is little information about whether the increased relative risk, if any, is confined to identifiable subgroups at elevated risk.

As the number of studies evaluating the long-term use of aspirin has expanded, it is now possible to evaluate the evidence in aggregate to more conclusively estimate the risk of hemorrhagic stroke, allowing a more informative benefit-risk assessment. This article reviews the available data in the published literature retrieved by bibliographic database (MEDLINE) search using the terms “aspirin,” “stroke/risk of stroke,” “subarachnoid hemorrhage,” and “intracerebral hemorrhage,” and supplemented by reference evaluations of published meta-analyses and reviews.

Pharmacological Basis for Aspirin Bleeding Risk
The antithrombotic effectiveness of aspirin is related to its inhibition of the cyclooxygenase (COX) enzyme that metabolizes arachidonic acid to a variety of prostanooids, including thromboxane A2.8 Platelet-derived cyclooxygenase-1 (COX-1) generates thromboxane A2, a potent vasoconstrictor and platelet agonist. The effect of aspirin on platelet COX-1 is irreversible, thus providing for once-daily low-dose effectiveness. With the inhibition of platelet COX-1 activity there is a decrease in platelet aggregation, leading to a reduced thromboembolic potential and a commensurate prolonged bleeding time. Thus, it is not surprising that the major risks
associated with aspirin relate to bleeding complications. Although there are studies that have suggested another salicylate antiplatelet agent, triflusal, may prevent vascular events with lower rates of hemorrhagic complications, aspirin remains the most widely used drug for this use. Recently, concerns have been raised regarding the potential for the selective COX-2 inhibitors to increase the risk of MI and ischemic stroke, leading some to suggest the use of aspirin as a means of attenuating this effect, despite the fact that such use would also likely blunt the gastrointestinal benefit afforded by COX-2 agent use.

**Data From Comprehensive Meta-Analyses**

Aspirin has been studied extensively in patients who have had a previous occlusive vascular event or are experiencing an acute evolving MI. Based on the rarity of hemorrhagic stroke and the fact that these studies were conducted principally to evaluate the effectiveness of aspirin in preventing future events, and powered accordingly, it is not surprising that despite the hundreds of thousands of patients studied, conclusions regarding the true risk of hemorrhagic stroke have been limited. As a result, emphasis in this review, as well as others, is placed on authoritative meta-analyses that have specifically examined the effect of aspirin on the incidence of hemorrhagic stroke.

There have been 6 meta-analyses conducted over a period from 1995 to 2003, including >315 627 patients. Although each of these evaluations include different studies, their conclusions, taken together, allow a more precise estimate of the true risks of aspirin. One of the most comprehensive of these analyses was performed by He et al. This meta-analysis, involving a wide variety of aspirin trials and cardiovascular indications (primary and secondary), integrated and assessed data from 55 462 participants in 16 trials that reported stroke subtypes (Table 1). Except for the British Doctors’ Trial (BDT), a placebo was used as the control in all of the trials in which participants were randomly assigned to either take or avoid aspirin. Hemorrhagic stroke events were reported in 13 of the 16 trials. In 11 of the 13 trials reporting hemorrhagic stroke, aspirin was associated with an increase in absolute risk of hemorrhagic stroke, but the increase was not statistically significant. The relative risk of hemorrhagic stroke was increased in these 11 trials, with a range of 1.08 to 4.09. No significant heterogeneity was noted in either absolute risk or relative risk across these studies (P=0.99 for both), suggesting that inclusion of both primary and secondary prevention studies is appropriate. The summary relative risk for hemorrhagic stroke with aspirin use was 1.84 (confidence interval [CI], 1.24 to 2.74) or an increased absolute risk of 12 events (CI 5 to 20) per 10 000 persons over 83 years of treatment or 0.4 excess events per 1000 users annually (P<0.001). The number needed to treat to cause 1 excess hemorrhagic stroke event was calculated to be 833 patients treated for 3 years. The absolute risk for hemorrhagic stroke did not appear to vary significantly according to pre-existing cardiovascular disease, age, sample size, dose of aspirin, or study duration, although the statistical power to detect such differences was low.

The findings presented by He et al are similar to the findings of the meta-analysis by Cappelleri of 5 randomized
controlled trials investigating the efficacy and safety of combined anticoagulant and/or antiplatelet therapy administered for up to 2.5 years after prosthetic heart valve replacement. In this evaluation, the estimated odds ratio for intracranial hemorrhage associated with aspirin monotherapy was 1.64 (CI, 0.72 to 3.74).

The Antithrombotic Trialists' Collaboration (ATT) performed a meta-analysis to evaluate the effects of antiplatelet therapy in patients at high risk for occlusive vascular events. This robust analysis included trials available by September 1997 and involved 287 studies, encompassing 135,000 participants. From trials reporting at least 1 hemorrhagic stroke, a proportional increase in the stratified odds ratio for fatal or nonfatal hemorrhagic stroke of 1.22 (CI, 1.03 to 1.44; P<0.01) was calculated. Although the majority of the studies included in the meta-analysis evaluated aspirin alone, some examined other antiplatelet agents. However, there is no evidence of a statistically significant difference in hemorrhage risk between these agents.

Serebruany conducted a meta-analysis of 50 trials that had clinical follow-up for at least 1 month and contained a full description of hemorrhagic complications. This analysis did not evaluate other risk factors or duration of dosing (beyond the 1-month minimal requirement for inclusion). The trials analyzed included a total of 338,191 patients, most of them with acute coronary syndrome (unstable angina and acute MI). Many of the studies involved aspirin, whereas the other studies involved a variety of other antiplatelet agents (eg, abciximab, ticlopidine, clopidogrel, etc). The objective of the analysis was to determine the frequency of bleeding complications based on the class and dose of antiplatelet agent used. The principal finding was that low-dose aspirin and dipyridamole therapy were associated with the lowest risk of bleeding complications. Furthermore, the risk of hemorrhagic stroke was constant across the low-dose aspirin range (<100 mg/d to 325 mg/d), with a rate of 0.3% (CI, 0.2% to 0.4%) for the 4 trials (12,661 patients) making up the data from 4052 patients from 6 trials comparing aspirin and oral anticoagulants in patients with atrial fibrillation. Rates of hemorrhagic stroke calculated for aspirin was 0.3 per 100 patient-years, and a hazard ratio was calculated between aspirin and oral anticoagulants of 1.84 (0.87 to 3.87).

### Data From the Individual Primary Prevention Trials

Six large-scale primary prevention trials, accounting for >94,000 patients, have been conducted to evaluate the clinical usefulness of aspirin in reducing the risk of MI in individuals at low to moderate coronary heart disease (CHD) risk. These studies, alone and collectively, provide insight into the benefit–risk profile of aspirin and expand the information on the potential risk of hemorrhagic stroke in the primary prevention setting. The initial 5 primary prevention trials, along with data from the Early Treatment Diabetic Retinopathy Study (ETDRS), as summarized by Hayden, are presented in Table 2.

In the Physicians' Health Study (PHS), the British Doctors’ Trial (BDT), and the Thrombosis Prevention Trial (TPT), rates for hemorrhagic stroke were higher among the aspirin-exposed participants than among controls, although these differences did not reach statistical significance. In the Hypertension Optimal Treatment (HOT) and Primary Prevention Project (PPP) trials, hemorrhagic stroke occurred almost equally in the intervention and control groups. Estimates of the rate of excess hemorrhagic stroke events attributed to aspirin were 0.20, 0.05, and 0.12 bleeding events per 1000 patients treated per year in the PHS, BDT, and TPT, respectively. In HOT and PPP, the approximate bleeding events caused per 1000 patients treated per year were 0.03 and 0.12, respectively. These event rates do not differ appreciably from those seen in the secondary prevention trials reviewed previously.

An effect of blood pressure, a known risk factor for hemorrhagic stroke, was not consistently demonstrated in these trials. In the HOT trial, hypertensive patients with baseline diastolic blood pressures between 100 and 115 mm Hg were evaluated. The patients were assigned initially to the antihypertension agent, felodipine, and were assigned to 1 of 3 diastolic blood pressure targets,


Meta-Analyses of Primary Prevention Studies

A number of meta-analyses have also been conducted using data from the primary prevention trials. Some of these analyses include the original larger trials (does not include ETDRS), whereas others do not include the more recent PPP trial. The Womens’ Health Study (WHS) has not been included in a meta-analysis at the time of this publication. The ATT has also recently undertaken a prospective meta-analysis of 5 primary prevention trials using individual patient data obtained from the investigators, with publication expected soon.

The meta-analysis of the 5 original primary prevention studies, which was conducted by Hayden et al in 2002, showed that aspirin reduces the risk of MI, with a summary OR of 0.72 (95% CI, 0.60 to 0.87). The analysis also demonstrated that aspirin was associated with an increased risk of hemorrhagic stroke (summary OR, 1.4; CI, 0.9 to 2.0). Estimates of the beneficial and harmful effects of aspirin were used to project impact of aspirin on populations of patients at different levels of 5-year risk for CHD. For patients with a 5% (high) risk, aspirin would be expected to prevent 14 CHD events and cause 0 to 2 hemorrhagic strokes; in patients with a 3% (moderate) risk, aspirin would prevent 8 CHD events and cause 0 to 2 hemorrhagic strokes; in patients with a 1% (low) risk, aspirin would prevent 3 CHD events and would cause 0 to 2 hemorrhagic strokes. Because no evidence from this, or other systematic reviews, demonstrates a relationship between underlying CHD risk and hemorrhagic stroke rates, the risk of hemorrhagic stroke was assumed to remain constant across the risk groups. Given the small number of hemorrhagic strokes in this series, the authors note that it is difficult to assess the contribution of other predisposing factors on the relationship between aspirin and hemorrhagic stroke.

Sudlow and Eidelman et al performed similar analyses using the same 5 primary prevention studies as Hayden and computed comparable effect estimate (OR, 1.4; 95% CI, 0.9 to 2.0 and 95% CI, 0.99 to 2.46) for hemorrhagic stroke, respectively, corresponding to an estimated annual excess risk of 0.1 events per 1000 users.

Earlier meta-analyses by Sanmuganathan et al and Hart et al using different subsets of the trials also had similar findings. More recently, Hart updated the evaluation by adding a trial in patients with diabetes (Early Treatment Diabetic Retinopathy Study [ETDRS]). A total of 52 251 participants made up this analysis (mean age, 57 years; mean

### TABLE 2. Hemorrhagic Stroke in Primary Prevention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Total treated</th>
<th>Total control</th>
<th>Odds Ratio (95% CI)</th>
<th>Events Caused (or Avoided) per 1000 Patients Treated With Aspirin/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians’ Health Study (PHS), 1989</td>
<td>231,1037</td>
<td>231,034</td>
<td>1.92 (0.95–3.86)</td>
<td>0.20</td>
</tr>
<tr>
<td>British Doctors’ Trial (BDT), 1988</td>
<td>13,3429</td>
<td>6,1710</td>
<td>1.08 (0.41–2.85)</td>
<td>0.05</td>
</tr>
<tr>
<td>Thrombosis Prevention Trial (TPT), 1998</td>
<td>3,1268</td>
<td>2,1272</td>
<td>1.51 (0.25–9.03)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment (HOT), 1998</td>
<td>14,9399</td>
<td>15,9391</td>
<td>0.93 (0.45–1.93)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>Primary Prevention Project (PPP), 2001</td>
<td>2,2226</td>
<td>3,2269</td>
<td>0.67 (NR)</td>
<td>(0.12)</td>
</tr>
<tr>
<td>Early Treatment Diabetic Retinopathy Study (ETDRS)*, 1992</td>
<td>NR/1856 (4.5%)</td>
<td>NR/1855 (3.8%)</td>
<td>1.17 (0.79–1.74) (99% CI)</td>
<td>(NR)</td>
</tr>
</tbody>
</table>

NR indicates not reported.

Adapted from Hayden et al 2002 with permission. Data from patients who received warfarin are not included.

Fatal or nonfatal stroke reported in trial.

≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg. When blood pressure was controlled (to pre-JNC-7 levels; individuals enrolled in the HOT trial would be considered prehypertensive based on JNC-7 recommendations), no differences in the rate of hemorrhagic stroke between the treatment and control groups were seen.

The number of women included in the original 5 primary prevention trials make it difficult to determine the impact of gender on risk. Only the HOT and PPP trials included women. With the recently reported Women’s Health Study, gender on risk. Only the HOT and PPP trials included

pre-hypertensive participants in the study, and aspirin reduced the risk of hemorrhagic stroke (summary OR, 1.4; CI, 0.9 to 2.0). Estimates of the beneficial and harmful effects of aspirin were used to project impact of aspirin on populations of patients at different levels of 5-year risk for CHD. For patients with a 5% (high) risk, aspirin would be expected to prevent 14 CHD events and cause 0 to 2 hemorrhagic strokes; in patients with a 3% (moderate) risk, aspirin would prevent 8 CHD events and cause 0 to 2 hemorrhagic strokes; in patients with a 1% (low) risk, aspirin would prevent 3 CHD events and would cause 0 to 2 hemorrhagic strokes. Because no evidence from this, or other systematic reviews, demonstrates a relationship between underlying CHD risk and hemorrhagic stroke rates, the risk of hemorrhagic stroke was assumed to remain constant across the risk groups. Given the small number of hemorrhagic strokes in this series, the authors note that it is difficult to assess the contribution of other predisposing factors on the relationship between aspirin and hemorrhagic stroke.

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Earlier meta-analyses by Sanmuganathan et al and Hart et al using different subsets of the trials also had similar findings. More recently, Hart updated the evaluation by adding a trial in patients with diabetes (Early Treatment Diabetic Retinopathy Study [ETDRS]). A total of 52 251 participants made up this analysis (mean age, 57 years; mean
follow-up, 4.6 years per patient), comprising ~240 000 patient-years observations. The results were consistent with the earlier analysis and indicated that the long-term use of aspirin increased the risk of hemorrhagic stroke in patients with and without manifest vascular disease (RR, 1.35; P = 0.03).

Based on these findings, it is clear that the risk of hemorrhagic stroke associated with aspirin use is comparable between the primary and secondary prevention studies. In addition, the risk of hemorrhagic stroke appears to be constant in the 2 populations across aspirin doses in the range of 75 to 325 mg/d.

Risk Factors for Spontaneous Hemorrhagic Stroke

In the hope that through better patient assessment and counseling the risk of hemorrhagic stroke with aspirin can be reduced, this section discusses the known risk factors and comments on possible relation to aspirin use. The key risk factors include previous stroke and cerebral bleeding and a history of hypertension. Other noteworthy risks may include age, race, and amyloid angiopathy. Neoplasm, vasculitis, bleeding disorders, vascular malformations and aneurysms, trauma, age, and anticoagulant use also may increase risk. Persons most at risk are, therefore, older adults, particularly those with high blood pressure, those who may be overweight, sedentary, smoke, or have diabetes, suggesting that specific recommendations can be made to ensure that aspirin use is avoided in “at-risk” patients. The challenge for developing label recommendations for aspirin use is that many of these same risk factors predispose patients to thromboembolic events for which aspirin is indicated. As such, the remaining sections of this article review possible risk factors and their utility for patient selection and risk assessment. It should be noted, however, that no specific risk factor has been shown to reliably alter the benefit–risk ratio for aspirin use.

History of Cerebrovascular Event

Generally, patients with a history of a previous cerebrovascular event are thought to be at higher risk of intracranial hemorrhage, independent of antithrombotic/anticoagulant use. Nonetheless, those are the people for whom aspirin is indicated and the available evidence suggests that the benefit–risk ratio is nonetheless favorable.

Hypertension

Individuals with hypertension have a substantial increase in risk of stroke. Studies have shown that hypertension is the main cause of hemorrhagic stroke in >85% of the cases. A review of 549 cases of hemorrhagic stroke demonstrated that both untreated and treated hypertension are significant risk factors for hemorrhagic stroke. The risk estimate for untreated hypertension was OR = 3.5 and CI = 2.3 to 5.2 (P < 0.0001), whereas the risk estimate for treated hypertension was OR = 1.4 and CI = 1.0 to 1.9 (P = 0.03).

Based on the ATT meta-analysis, antplatelet therapy use in patients who have experienced a previous thromboembolic event, who also had a history of elevated blood pressure, results in an absolute reduction in vascular events, including ischemic stroke, of 4% compared with placebo. Thus, for secondary prevention, antiplatelet therapy can be recommended regardless of a history of hypertension, because the magnitude of the absolute benefit is greater than the risk. In primary prevention trials, aspirin regardless of blood pressure status reduced the risk of nonfatal MI, in men and stroke rates in women, suggesting that antiplatelet therapy should be limited to those when the risk for an event is moderate or greater. Likewise, reducing blood pressure should be the focus of any risk reduction strategy.

Age, Race, and Dose

The incidence of primary hemorrhagic stroke increases with age. Dyken reported that the risk increases with increased age and doubles with every decade after age 55.

The relationship between age and intracranial bleeding is clear from the results of the large Stroke Prevention in Atrial Fibrillation II trial, with an increased incidence of intracranial hemorrhage seen in the older participants. The rate of intracranial hemorrhage with aspirin use was 0.8% per year in patients older than age 75 years versus 0.2% per year in patients age 75 years and younger.

The risk of hemorrhagic stroke is increased in certain racial groups, eg, blacks, and may parallel increased hypertension risk in this population.

There are limited data available from randomized trials comparing doses within the 75-mg to 325-mg range to provide a meaningful comparison regarding risk of hemorrhagic stroke. The only relevant controlled trial evaluated 2849 patients scheduled for endarterectomy who were randomized to receive 81 mg, 325 mg, 650 mg, or 1300 mg aspirin daily starting before surgery and continued for 3 months. In this study, hemorrhagic stroke was less frequent in the 81-mg and 325-mg groups than that reported for the 650-mg and 1300-mg groups, although not significant (RR, 1.68; 95% CI, 0.77 to 3.68; P = 0.18).

Amyloid Accumulation

Hemorrhagic stroke has also been associated with accumulation of amyloid within the cerebral artery walls, making them more prone to bleeding, particularly in the elderly. The predominance of aspirin-induced hemorrhages in the lobar areas in the study by Wong suggests the possible presence of a vascular abnormality, such as amyloid angiopathy, which is known to affect older patients. Nonetheless, the relationship between amyloid angiopathy induced bleeding and aspirin use remains unclear.

Epistaxis

A history of epistaxis while receiving aspirin has been identified as a possible independent risk factor for hemorrhagic stroke. Saloheimo et al evaluated 98 patients, between the ages of 36 and 90 years, with primary intracerebral hemorrhage. Their findings demonstrated that epistaxis might increase risk of intracerebral hemorrhage in subjects using high doses of aspirin (OR of epistaxis, 2.75; 95% CI, 1.11 to 6.81; OR of aspirin use, 14.7; 95% CI, 2.03 to 106).

Other Risk Factors

Berry aneurysms may be associated with use of aspirin, but this association needs to be verified by further epidemiological study. Other independent risk factors for intracerebral hemorrhage include a history of hypertension, diabetes mellitus, hyperlipidemia, anemia, and cigarette smoking.
hemorrhage might include epilepsy or strenuous physical exertion.43

Conclusions
Aspirin is a valuable and cost-effective antiplatelet agent with an excellent benefit–risk profile across both the secondary and primary prevention indications. Antiplatelet therapy is associated with an increased risk of bleeding, although low-dose aspirin is associated with the lowest risk. Because intracranial and extracranial hemorrhage risk associated with aspirin appears constant and independent of CHD risk, the assessment as to the relative benefits and harm must consider the absolute coronary heart risk of the patient. When aspirin is used for prevention of recurrent cardiovascular events, the benefits of aspirin clearly outweigh possible harm from a major hemorrhage. In primary prevention, the balance between benefit and harm is equally clear for patients when the CHD risk is moderate to high. Interesting new findings from the Women’s Health Study suggest that in apparently healthy women at low risk, significant benefit in reducing total stroke can also be achieved, suggesting that a benefit in reducing ischemic stroke outweighs the potential, although not statistically significant, increase in hemorrhagic stroke. Furthermore, the benefit–risk relationship can be enhanced by greater education and research regarding hemorrhagic stroke and its causes. Blood pressure control may have an impact on lowering the occurrence of these events.

The available evidence supports a reasonable estimate of the risk of hemorrhagic stroke associated with the use of aspirin therapy in primary prevention patients at risk for CHD being 0.2 events per 1000 patient-years. That is, for every 1000 patients treated for a 5-year period, aspirin therapy would be expected to result in 1 excess hemorrhagic stroke compared with a benefit of ~14 myocardial infarctions prevented in patients at moderate risk for CHD (5% to 10% 5-year risk). Based on the rarity of hemorrhagic stroke risk, concerns about this risk should not dissuade appropriate patients from using low-dose aspirin. Patients being considered for aspirin therapy must be clinically evaluated to determine whether the benefit of treatment exceeds the risks. The factors that may increase the risk of hemorrhagic stroke must be considered for all patients being evaluated for antiplatelet therapy. As such, those risk factors that may elevate the risk for hemorrhagic stroke (high doses of aspirin, increased patient age, and uncontrolled hypertension) must be taken into account for proper selection and de-selection of patients for therapy. Choosing doses between 75 mg and 325 mg per day provides an optimal benefit to risk relationship. In addition, counseling patients on the possible signs and symptoms associated with adverse events, such as hemorrhagic stroke, and the need for prompt medical action is an important part of the medical management of patients being considered for aspirin therapy.

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