



## 15 ATTACHMENT 2

### 15.1 Intracranial Bleeding (Hemorrhagic Stroke)

The decision as to which patients to treat with ASA must weigh the benefits of chronic ASA therapy against the possible risks associated with its use, including the risk of hemorrhage. The most serious risk associated with the use of ASA is the potential increased risk of intra- and inter-cranial bleeding, or hemorrhagic stroke (ISIS-2, 1988; UK-TIA Study Group, 1991; Juul-Möller et al., 1992; Steering Committee of the Physicians Health Study, 1989; Stroke Prevention in Atrial Fibrillation Investigators, 1991; Antithrombotic Trialists' Collaboration, 2002). Although a number of studies have suggested an exceedingly small increase risk of such events with ASA, limitation of statistical power of the studies has prevented definitive conclusions from being made. As the database of studies evaluating the long-term use of ASA has grown, 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.

Although the risk of hemorrhagic stroke is extremely low, its seriousness necessitates that patients should be selected for therapy based on the expected benefit significantly exceeding the risk. As the benefit, in terms of absolute risk reduction, is lower in primary prevention, careful attention to the risk of hemorrhagic stroke and an understanding of the factors that increase this risk are warranted before wide-scale recommendations regarding patient selection and labeling can be made. This document presents an update of the data available in the literature, as well as post-marketing surveillance information provided by Bayer HealthCare, to provide greater clarity regarding the risks of ASA with respect to hemorrhagic stroke and insights regarding patient selection and labeling.

#### 15.1.1 Pharmacologic Mechanism of ASA Increase in Bleeding / Hemorrhage

It is well recognized that the cardioprotective effectiveness of ASA is related to its suppression of the synthesis of the proaggregatory factor thromboxane A<sub>2</sub> (Mueller, 2001). The effect of ASA on platelet COX is irreversible, thus providing for once-daily low-dose effectiveness. Based on this mechanism, it is not surprising that the major risks associated with ASA relate to bleeding complications. Potential bleeding in the brain is of significant consequence, and hence, a concern with any anticoagulant/antithrombotic treatment.

#### 15.1.2 Intracerebral Bleeding (Hemorrhagic Stroke) - Overview

Intracerebral bleeding events have been reported in individuals using ASA for prevention of cardiovascular events, both for primary prevention and secondary prevention. These events have been elicited from publications of individual clinical studies, a number of meta-analyses, and case reports, with the most reliable information being derived from placebo controlled studies. Based on the rare nature of these reports, it is appropriate to consider all uses of low-dose ASA when evaluating the potential for hemorrhagic stroke. For this reason, we carefully review findings from all chronic uses studies, in the interest of establishing a benefit-risk relationship. Not surprisingly, the largest number of

patients comes from the secondary prevention studies, and since these patients would be expected to have a risk of hemorrhagic stroke at least as great as those who might be candidates for primary prevention, these data provide meaningful insight.

In each of the published trials, the absolute numbers of cases of intracerebral bleeding are small, leading to wide confidence intervals around the risk estimates. The uncertainty is completed by diagnostic inaccuracy, as in most trials few patients with stroke underwent CT scanning. In addition, there is little information about whether the relative risk, if any, is confined to identifiable subgroups at elevated risk, such as the elderly. Similarly, there is significant ambiguity around cases derived from post-marketing surveillance. Nonetheless, a review of the published literature, especially those of meta-analyses, and a review of the post-marketing surveillance reports provide the best estimate of risk of hemorrhagic stroke with the use of ASA and should guide regulatory decision-making.

### 15.1.3 Meta-Analyses

ASA has been studied extensively in patients that have had a previous CHD event or are experiencing an acute evolving MI. As these studies are powered to evaluate the effectiveness of ASA, and the fact that hemorrhagic stroke is extremely rare, it is not surprising that in spite of 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 a number of well-regarded meta-analyses that have specifically examined the effect of ASA on the incidence of hemorrhagic stroke. Based on the rarity of events in individual studies as well as case series based on specific inclusion criteria, many of these analyses have included both primary and secondary prevention studies to more precisely estimate the risk of hemorrhagic stroke associated with ASA use. Ironically, in spite of their size, many of these analyses fail to be conclusive.

The meta-analyses that were reviewed for this summary and their risk estimates for hemorrhagic stroke are summarized in Table 42.

**Table 42: Estimated Odds Ratio for Hemorrhagic Stroke/Intracranial Hemorrhage Associated with ASA Use**

| Study               | Odds Ratio, (CI)   |
|---------------------|--------------------|
| He, et al. (1998)   | 1.84 (1.24 – 2.74) |
| Cappelleri (1995)   | 1.64 (0.72 – 3.74) |
| ATT (2002)          | 1.22 (1.03 – 1.44) |
| Hankey (2000)       | 0.82 (0.53 – 1.27) |
| Wald (2003)         | 1.52 (0.9 – 2.46)  |
| Van Walraven (2002) | 1.84 (0.87 – 3.87) |

A comprehensive meta-analysis of hemorrhagic stroke was performed by He and colleagues (1998) involving a wide variety of ASA trials and cardiovascular indications,

including two primary prevention populations, BDT and PHS. This meta-analysis included an evaluation of 16 trials (including 14 secondary prevention trials) that reported stroke subtypes involving more than 50,000 participants (presented in the Table 43). Placebo was used as the control in all of the trials except for the BDT, in which participants were randomly assigned to either take or avoid ASA. A total of only 108 hemorrhagic stroke events were reported from 13 trials involving 55,462 participants. In 11 of the 13 trials reporting hemorrhagic stroke, ASA was associated with an increase in absolute risk of hemorrhagic stroke, although none reached the level of statistical significance. The relative risk of hemorrhagic stroke was also increased in these 11 trials, with a range of 1.08 to 4.09. There was no significant heterogeneity in absolute risk or relative risk among these studies ( $p=0.99$  for both). The relative risk for hemorrhagic stroke with ASA use was 1.84 (CI=1.24-2.74), or an increased absolute risk of 12 events (CI=5-20) per 10,000 persons over approximately 3 years of treatment, or about 0.4 excess events per 1,000 users annually ( $p<0.001$ ). The number needed to treat to cause 1 excess hemorrhagic stroke event was calculated to be 833. The absolute risk for hemorrhagic stroke did not appear to vary significantly according to pre-existing CVD, mean age, sample size, dose of ASA or study duration, although the statistical power to detect such differences was low.

**Table 43: The Randomized Controlled Trials of ASA to Prevent MI and Ischemic Stroke**

| Source, year   | No. of Participants |  | Age, y (mean) | Male (%) | Preexisting Condition                                |
|--|---------------------|--|---------------|----------|--|
|  | ASA/Control *       |  |               |          |  |
| Fields, 1977   | 88/90               |  | 61            | 66       | TIA  |
| Fields, 1978   | 65/60               |  | 61            | 74       | TIA  |
| Elwood and Sweetnam, 1979                                  | 832/850             |  | 57            | 85       | MI   |
| Bousser, 1983  | 198/204             |  | 64            | 68       | Cerebral ischemia                                    |
| Sorensen, 1983   | 101/102             |  | 59            | 73       | TIA  |
| Britton, 1987  | 253/252             |  | 68            | 62       | Cerebral infarction                                  |
| ISIS-2 Collaborative Group, 1988                           | 8,587/8,600         |  | 62            | 77       | Acute MI   |
| Peto, 1988 (BDT)**   | 3,429/1,710         |  | 60            | 100      | Healthy  |
| Steering Committee of the PHS Research Group, 1989 (PHS)** | 11,037/11,034       |  | 53            | 100      | Healthy  |
| Petersen, 1989   | 336/336             |  | 75            | 54       | Atrial fibrillation                                  |
| SPAF Investigators, 1991                                   | 552/568             |  | 67            | 70       | Atrial fibrillation                                  |
| SALT Collaborative Group, 1991                             | 676/684             |  | 66            | 66       | TIA or minor ischemic stroke                         |
| UK-TIA Study Group, 1991                                   | 815/814             |  | 60            | 72       | TIA  |
| Juul-Möller, 1992  | 1,009/1,026         |  | 67            | 52       | Stable angina  |
| EAFT Study Group, 1993                                     | 404/378             |  | 73            | 56       | Atrial fibrillation and TIA or minor ischemic stroke |
| Cote, 1995   | 188/184             |  | 67            | 47       | Carotid stenosis                                     |
| Total/Means  | 28,570/26,892       |  | 59            | 86       | ---  |

\* Data are number of participants in ASA group/number of participants in control group; \*\* Primary prevention studies are highlighted; (He et al., 1998)

The findings presented above corroborate the analysis of 5 studies investigating the efficacy and safety of combined anticoagulant and/or platelet therapy administered for up to 2.5 years after mechanical heart valve replacement (Cappelleri et al., 1995). In this evaluation, the estimated odds ratio for intracranial hemorrhage associated with ASA monotherapy was 1.64 (CI=0.72-3.74).

The Antithrombotic Trialists' Collaboration (ATT, 2002) meta-analysis was performed to evaluate the effects of antiplatelet therapy in patients at high-risk of occlusive vascular events. This robust analysis included trials available through September 1997 and involves 287 studies and 135,000 participants. From the trials reporting at least one hemorrhagic stroke, a proportional increase in fatal or nonfatal hemorrhagic stroke of 1.22 (CI=0.03-0.44,  $p<0.01$ ) was observed. While the majority of the studies evaluated

ASA alone, some of the studies in this series examined other antiplatelet agents, demonstrating no evidence of a difference in hemorrhage risk between these agents.

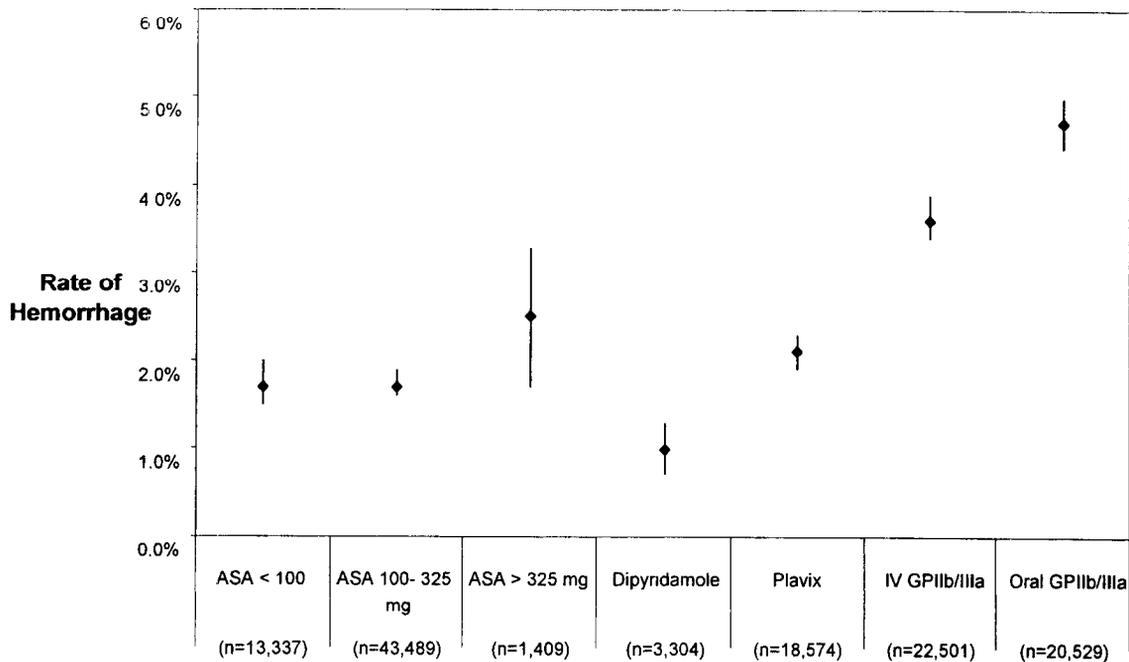
To further evaluate the comparative risks of hemorrhagic stroke associated with a variety of antiplatelet agents, Serebruany, et al (2004) conducted a meta-analysis to evaluate the risk of bleeding complications associated with the therapeutic category. Their analysis included 50 trials that had clinical follow-up for at least 1 month and contained a full description of hemorrhagic complications. The trials analyzed included a total of 338,191 patients, most of them with acute coronary syndrome (unstable angina and acute MI). More than half the studies (28) involved ASA, with the other studies involving a variety of other agents (e.g., 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 major finding of the analysis was that low-dose ASA and dipyridamole therapy were associated with the lowest risk of bleeding complications. Furthermore, the risk of hemorrhagic stroke was constant across the low-dose range (<100 mg/day to 325 mg/day), with the risk of a bleeding stroke of 0.3% in both the < 100 mg dose of ASA and the 100-325 mg dose groups, suggesting a flatness of the dose response curve in this range (See Table 44). The risk of hemorrhagic stroke was found to increase to 1.1% in doses above this range (see Figure 19). The differences in the risk for hemorrhagic stroke associated with use of different antiplatelet agents varied, with the doses of < 100 to 325 mg demonstrating the lowest risk for hemorrhagic stroke. This analysis did not evaluate other risk factors or duration of dosing (beyond the one month minimal requirement for inclusion).

**Table 44: Risk of Bleeding Complications with ASA**

| ASA Dose   | No of Trials Reported | No. of patients (n) | Rate (f) | 95% C.I.     |
|------------|-----------------------|---------------------|----------|--------------|
| < 100 mg   | 4                     | 12,639              | 0.3%     | (0.2%, 0.4%) |
| 100-325 mg | 15                    | 152,955             | 0.3%     | (0.2%, 0.3%) |
| > 325 mg   | 3                     | 2,224               | 1.1%     | (0.7%, 1.5%) |

*Adapted from Serebruany, 2004*

**Figure 19: Weighted Combination of Major Bleeding Events with 95% CI Across Treatment Group**



*Adapted from Serebrauany, 2004*

Hankey and colleagues (2000) performed a meta-analysis of 4 trials (CAPRIE, Tohgi, Schoop, TASS) including 22,656 patients, with an average duration of treatment of 2 years. The purpose of the review was to compare the efficacy and safety of thienopyridines (ticlopidine or clopidogrel) with ASA at doses of 325 to 1500 mg/day in patients at high-risk of vascular disease. The thienopyridines were found to be only modestly more effective than ASA in preventing serious vascular events in these patients. In addition, there was no difference between the thienopyridines and ASA in the odds of experiencing an intracranial hemorrhage (0.3% for thienopyridine vs. 0.4% for ASA; OR=0.82, CI=0.53-1.27), and again no indication of a dose relationship.

A meta-analysis of 15 randomized primary and secondary prevention trials of ASA (50-125 mg/day) by Wald calculated a summary odds ratio for hemorrhagic stroke of 1.52 (CI=0.94-2.46) (Wald and Law, 2003). The studies selected were of at least 6 months duration. Four of the studies included healthy adults, nine included patients with a history of ischemic heart disease, and two included patients with atrial fibrillation. The meta-analysis demonstrated a 32% reduction of ischemic heart disease events and a 16% reduction of strokes, thus concluding that a positive benefit-risk relationship.

#### 15.1.4 Intracerebral Bleeding Data from Primary Prevention Trials

The 5 primary prevention trials establish the clinical benefit of ASA in reducing the risk of MI in individuals at low to moderate CHD risk patients. Likewise, these studies

provide important scientific evidence as it relates to benefit-risk profile, and expand the information on the potential risk of hemorrhagic stroke associated with ASA. Data relevant to hemorrhagic stroke from the 5 primary prevention trials are summarized below in Table 45.

**Table 45: Hemorrhagic Stroke / Intracranial Hemorrhage in Primary Prevention Trials**

|     | Events/Patients (%)  |                      | Odds ratio (95%CI) | Events caused (or avoided) per 1000 patients treated with ASA per year |
|-----|----------------------|----------------------|--------------------|--|
|     | ASA                  | Control              |                    |  |
| PHS | 23/11,037<br>(0.21%) | 12/11,034<br>(0.11%) | 1.92 (0.95 – 3.86) | 0.20   |
| BDT | 13/3,429<br>(0.38%)  | 6/1,710<br>(0.35)    | 1.08 (0.41 – 2.85) | 0.05   |
| TPT | 3/1,268<br>(0.24%)   | 2/1,272*<br>(0.16%)  | 1.51 (0.25 – 9.03) | 0.12   |
| HOT | 14/9,399<br>(0.15%)  | 15/9,391<br>(0.16%)  | 0.93 (0.45 – 1.93) | (0.03)   |
| PPP | 2/2,226<br>(0.08%)   | 3/2,269<br>(0.13%)   | 0.67 (NR)          | (0.12)   |

Adapted from Hayden, 2002

PHS=Physicians' Health Study, BDT=British Doctor's Trial, TPT=Thrombosis Prevention Trial, HOT=Hypertension Optimal Treatment, N/R=Not Reported

\* Data from patients who received warfarin are not included

The event rates for hemorrhagic stroke were higher among the ASA-exposed participants than controls in PHS, TPT and BDT, although these differences did not reach statistical significance in any single trial. In BDT, the cause of most of the strokes reported (>60%) was unknown. In both the HOT and PPP trials, hemorrhagic stroke occurred almost equally in the intervention and control groups. The estimates of the rate of excess events attributed to ASA in hemorrhagic stroke and intracranial hemorrhage were 0.20, 0.05, and 0.12 bleeding events per 1,000 patients treated per year in the PHS, BDT, and TPT, respectively. In the HOT and the PPP, the approximate bleeding events avoided per 1,000 patients treated per year were 0.03 and 0.12, respectively. These adverse event rates do not differ appreciably from those seen in the secondary prevention trials.

The effect of blood pressure on the occurrence of hemorrhagic stroke was not consistently demonstrated in these trials. Interestingly, in the HOT trial, where blood pressure was controlled, although by today's standards would be considered elevated, no difference in the occurrence of hemorrhagic stroke between the treatment and control groups was seen. In all studies, the difference in the percent of patients experiencing a

hemorrhagic stroke or intracranial bleed (ASA vs. placebo) did not reach statistical significance, due to the very rare occurrence of these events.

The HOT and PPP trials included women providing an opportunity to evaluate risk of hemorrhagic stroke in this sub-group. A sub-group analysis of the HOT data to evaluate the influence of gender on the risks and benefits of ASA chemoprevention was undertaken by Kjeldsen and colleagues (2000). With the limited number of women included in the primary prevention trials, it is difficult to determine whether gender impacts the risks. The Women's Health Study should provide further clarity regarding the risks and benefits of low-dose ASA in women, although the dose in the study is lower than being requested in the Citizen Petition (Rexrode et al., 2000).

### 15.1.5 Meta-Analyses of Primary Prevention Studies

A number of meta-analyses have been conducted using data from the primary prevention trials, including those that included all 5 trials, as well as earlier analyses which did not include the PPP trial (Hart, 2000). The ATT Collaboration has also recently undertaken a prospective meta-analysis of the 5 primary prevention trials using individual patient data obtained from the investigators, with publication expected shortly (data to be submitted separately).

**Table 46: Estimated Odds Ratio for Hemorrhagic Stroke/Intracranial Hemorrhage Associated with ASA Use from Published Meta-Analyses**

| Meta-Analysis                       | Odds Ratio, (CI)   |
|-------------------------------------|--------------------|
| Hayden, (2002)                      | 1.4 (0.9 – 2.0)    |
| Sudlow (2001)                       | 1.4 (0.9 – 2.0)    |
| Eidelman (2003)                     | 1.56 (0.99 – 2.46) |
| Hart (2000)<br>(PHS, BDT, TPT, HOT) | 1.36 (0.88 – 2.1)  |

Hayden (2002) and colleagues meta-analysis of the 5 primary prevention studies demonstrated that ASA reduces the risk of MI with a summary odds ratio of 0.72 (95% CI=0.60-0.87) and was associated with an increased risk of hemorrhagic stroke, with a summary odds ratio of 1.4 (CI=0.9-2.0). Based on these findings, estimates of the beneficial and harmful effects of ASA can be modeled to estimate its impact on populations of patients with different levels of risk for CHD. As no evidence from this or other systematic reviews demonstrated a relationship between underlying CHD risk and hemorrhagic stroke rates, the risk of hemorrhagic stroke was assumed to remain constant across the risk groups. For patients with a 10% risk for CHD events over 10 years (moderate-risk), ASA would prevent 14 CHD events and would cause 0 to 2 hemorrhagic strokes; for patients with a 6% risk for CHD events over 10 years (low-moderate-risk), ASA would prevent 8 CHD events and would cause 0-2 hemorrhagic strokes; for patients with a risk of 2% over 10 years (low-risk), ASA would prevent 3 CHD events and would

cause 0 to 2 hemorrhagic strokes. 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 ASA and hemorrhagic stroke.

**Table 47: Benefit-Risk Analysis with ASA Therapy at Different Levels of Risk for CHD Events**

|                                  | Estimated 10-Year Risk for CHD Events at Baseline |          |           |
|----------------------------------|---|----------|-----------|
|                                  | 2%  | 6%       | 10%       |
| CHD events avoided               | 3 (1-4)   | 8 (4-12) | 14 (6-20) |
| Hemorrhagic Strokes precipitated | 1 (0-2)   | 1 (0-2)  | 1 (0-2)   |

*Adapted from Hayden et al., 2002*

Sudlow (2001) also performed an analysis using the 5 primary prevention studies and obtained a similar odds ratio, 1.4 (CI=0.9-2.0) for hemorrhagic stroke. This corresponds to an estimated annual excess risk of 0.1 events per 1,000 users.

Eidelman and colleagues' (2003) meta-analysis of the 5 primary prevention trials found a borderline statistical significance for hemorrhagic stroke (RR=1.56; 95% CI=0.99–2.46).

The ATT Collaboration (FDA AC Presentation, December 8, 2003) comprehensive meta-analysis using raw data from the same 5 primary prevention trials should be viewed as most informative. These data demonstrate no differences in the risk of hemorrhagic stroke between the secondary and primary prevention patient populations and confirm the low-risk observed by others. These data are expected to be available for FDA review shortly.

Earlier meta-analyses utilizing the initial 4 primary prevention trials had similar findings. The 4 primary prevention studies included in these analyses were the PHS, BDT, TPT and the HOT study. Sanmuganathan and colleagues' (2001) analysis calculated a combined odds ratio for risk of bleeding complications with ASA. Combined data on harms were placed into a single category of "major bleeding events" induced, and they calculated that the number of bleeding events induced equaled the number of cardiovascular events averted when the cardiovascular event rate was 0.22% per year. They 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, equivalent to an event rate of 0.6% per year for CHD. They concluded that ASA was appropriately safe for persons with a risk for CHD events exceeding 1.5% per year and not appropriate safe for persons with a risk of less than 0.5% per year.

Hart and colleagues pooled results from the first 4 primary prevention trials (PHS, BDT, TPT and HOT) and estimated that the relative risk for hemorrhagic stroke due to long-term ASA use was 1.36 (CI=0.88-2.1). Hart also updated the evaluation to include 5 trials, the first 4 of the 5 primary prevention trials, and a trial in patients with diabetes ETDRS (see Table 48), which included 52,251 participants with a mean age of 57 years who were followed up for about 240,000 patient-years observation (mean follow-up was

4.6 years per patient). Women comprised 20% of the participants. The estimated long-term use of ASA (mean 4.6 years) increased the incidence of hemorrhagic stroke in patients with and without manifest vascular disease (RR=1.35; p=0.03).

**Table 48: Randomized Clinical Trials of ASA Therapy for Primary Prevention**

| Study               | Sample Size | Population Category                 | Mean Age, y | ASA Dose mg/u | Women (%) | Participants with Hypertension (%) | Mortality Rate (%/y) |
|---------------------|-------------|-------------------------------------|-------------|---------------|-----------|------------------------------------|----------------------|
| PHS                 | 22,071      | Healthy Male Physicians             | 53          | 325           | 0         | 12                                 | 0.4                  |
| BDT                 | 5,139       | Male Physicians                     | 61          | 500           | 0         | 10                                 | 1.6                  |
| ETDRS               | 3,711       | Patients with Diabetes              | 50          | 650           | 44        | 44                                 | 3.0                  |
| TPT                 | 2,540       | Patients with Coronary Risk Factors | 57          | 75            | 0         | N/R                                | 1.3                  |
| HOT                 | 18,790      | Patients with Hypertension          | 62          | 75            | 47        | 100                                | 0.9                  |
| All Clinical Trials | 52,251      |                                     | 57          |               | 20        | 47                                 | 1.0                  |

PHS: (Steering Committee of the Physicians' Health Study, 1989), BDT: (Peto et al., 1988), ETDRS: (ETDRS Study Investigators, 1992), TPT: (The Medical Research Council's General Practice Research Framework, 1988), HOT: (Hansson et al., 1998), N/R=Not Reported (Hart, 2000)

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

#### 15.1.6 Post-Marketing Surveillance of Hemorrhagic Stroke

Post-marketing surveillance and risk assessment programs have been found to be useful in identifying adverse events that, based on their rarity, are not readily detected in clinical trials and case series. Spontaneously reported adverse event data are thus helpful in identifying signals that may potentially impact the safe use of the product. The interpretation and usefulness of spontaneous adverse event report data in assessing risk is limited by a number of factors such as the voluntary nature for reporting adverse events, the limitations in the quality of the information received, and the inability of verifying information on adverse event reports including the association of the event and drug. Therefore, it is important to note the information should not be used to establish true incidence rates.

An analysis of spontaneous cerebral bleeding cases for ASA treated patients was undertaken by Bayer HealthCare. The objective of the analysis was to evaluate the rate of cerebral bleeding events for spontaneous cases treated with ASA  $\leq$  100 mg compared with cases treated with ASA  $>$  100 mg and to consider risk factors. This analysis included all reports of adverse event cases treated with ASA in which the indication was known (antiplatelet or analgesic use) as received by Global Drug Safety. The data evaluated cases up to December 2, 2003. Cases that reported ASA overdose, or exceeding the recommended dose, were excluded. The MedDRA reference terms were used to identify cases.

A total of 1,976 adverse event reports associated with ASA  $\leq$  100 mg and 4,091 AE reports associated with ASA  $>$  100 mg were identified. Of these cases, 66 cases treated with ASA  $\leq$  100 mg and 383 cases treated with ASA  $>$  100 mg were excluded from the analysis due to exceeding the recommended dose, leaving 1,910 cases treated with ASA  $\leq$  100 mg and 3,708 cases treated with ASA  $>$  100 mg for the analysis.

When reporting rates are evaluated in relationship to sales volume, patient exposure days can be converted into patient exposure years (by dividing by 365.25). As shown in Table 49, the reporting rates calculated worldwide are much lower than those given in the incidence-prevalence database (IRIS/CASIS, 3/20/2000).

**Table 49: Worldwide Reporting Rates of Hemorrhagic Stroke Cases Based on Patient Exposure as Derived from Sales Data**

|                  | ASA $\leq$ 100 mg           |                              | ASA $>$ 10 mg              |                             |
|------------------|-----------------------------|------------------------------|----------------------------|-----------------------------|
|                  | No. Cases/py                | No. Cases/10 <sup>7</sup> py | No. Cases/py               | No Cases/10 <sup>7</sup> py |
| Antiplatelet Use | 23 / 12.461*10 <sup>7</sup> | 2                            | 22 / 4.325*10 <sup>7</sup> | 5                           |
| Pain Use         | 15 / 12.461*10 <sup>7</sup> | 1                            | 9 / 4.325*10 <sup>7</sup>  | 2                           |
| Both Indications | 38 / 12.461*10 <sup>7</sup> | 3                            | 31 / 4.325*10 <sup>7</sup> | 7                           |

*Bayer HealthCare Data on File, 2003 py = patient-years*

Results of the analysis demonstrated that from those cases associated with antiplatelet use, 1.9% (23/1,229) of the cases treated with ASA  $\leq$  100 mg and 2.7% (22/819) of the cases treated with ASA  $>$ 100 mg reported cerebral bleeding events. For those cases associated with analgesic use, 2.2% (15/681) of the cases treated with ASA  $\leq$  100 mg and 0.4% (9/2,398) of cases treated with ASA  $>$  100 mg reported cerebral bleeding cases.

**Table 50: ASA Spontaneous Reports Distribution**

| Population                          | Indication       | ASA ≤ 100 mg         | ASA > 100 mg         |
|-------------------------------------|------------------|----------------------|----------------------|
| All Cases                           | Antiplatelet use | 1229 / 1,910 (64.3%) | 819 / 3,708 (22.1%)  |
|                                     | Analgesic use    | 681 / 1,910 (35.7%)  | 2398 / 3,708 (64.7%) |
|                                     | Unknown          |                      | 491 / 3,708 (13.2%)  |
| Cases with cerebral bleeding events | Antiplatelet use | 23 / 38 (60.5%)      | 22 / 33 (66.7%)      |
|                                     | Analgesic use    | 15 / 38 (39.5%)      | 9 / 33 (27.3%)       |
|                                     | Unknown          |                      | 2 / 33 (6.1%)        |

*Bayer HealthCare, Data on File, 2003*

The median age of the spontaneous cases associated with antiplatelet use was higher than the cases associated with analgesic use, although cases with cerebral bleedings were in the same age median for both indications. The proportion of cases with cerebral bleeding events was higher in those cases with a known risk factor. The risk factors included concomitant drug use (NSAIDs, antithrombotics, or sympathomimetics) and/or underlying diseases (hypertension, aneurism, stroke, or bleeding disorders) that are associated with bleedings. Looking at cases where aspirin was used for antiplatelet effects, results of the analysis demonstrated that from those cases treated with ASA ≤ 100 mg, 78.3% of those cases with cerebral bleeding (18/23) presented with risk factor(s) vs. 21.7% without a risk factor. Similarly, the cases treated with ASA > 100 mg demonstrated that 72.7% of those cases with cerebral bleeding (16/22) presented with risk factor(s) vs. 27.3% without a risk factor (See below).

The analysis of the cases from the Bayer HealthCare database is suggestive of confounding by underlying disease and risk factors and is not suggestive of a dose effect. As such, these findings are consistent with the findings from the controlled studies and meta-analyses reviewed above.

The analysis did not show an increased reporting of cerebral bleeding events for ASA and, if one considers advanced age as a risk factor, the analysis confirmed that all patients evaluated (except one patient with insufficient data on age, medical history and drug treatment) had one or more risk factors. These data along with other data regarding risk factors associated with stroke, as outlined below, should prove helpful in developing labeling to guide physicians and patients regarding the risk of hemorrhagic stroke in the primary prevention population.

#### 15.1.7 Risk Factors for Spontaneous Intracerebral Hemorrhage

Hemorrhagic stroke accounts for 10 to 15% of all cases of stroke. The bleeding usually occurs because of a rupture in arterial walls that are already weakened by high blood pressure. In addition to hypertension, primary risks include age, race, and amyloid accumulation. Secondary risks include neoplasm, vasculitis, bleeding disorders, prior

embolic infarction, aneurysm, vascular malformation, trauma, age and concomitant drugs causing bleeding. Persons most at risk for stroke are therefore, older adults, particularly those with high blood pressure, who are overweight, sedentary, smoke, or have diabetes.

### 15.1.7.1 Hypertension

Individuals with hypertension have up to ten times the normal risk of stroke, depending on the severity of the blood pressure. Some studies have shown that hypertension is the main cause of hemorrhagic stroke in over 85% of the cases (Kumral et al., 1998). Gorelick and colleagues (Gorelick et al., 1999) evaluated a hospital-based case control study in Australia and presented the various risks of those with hypertension-associated hemorrhagic stroke in the study. The risks are presented in Table 51. Hypertensive patients that had stopped taking medication were more than twice as likely to have a hemorrhagic stroke compared to hypertensive patients who were taking their medications. Patients who died in the study were more than 5 times as likely to have hemorrhagic stroke due to hypertension compared to survivors (Thrift, 1998). These risk estimates were comparable to the estimates from a review of 549 cases of hemorrhagic stroke (Woo et al., 2004) that demonstrated that untreated and treated hypertension was found to be a significant risk factor for hemorrhagic stroke. The risk estimate for untreated hypertension was OR=3.5, CI=2.3–5.2,  $p < 0.0001$ , while the risk estimate for treated hypertension was OR=1.4, CI=1.0–1.9,  $p = 0.03$ , thereby further highlighting the importance of blood pressure control.

**Table 51: Odds Ratios for Patients with Hypertension-associated Hemorrhagic Stroke**

|                                  | Odds Ratio | 95% Confidence Interval |
|----------------------------------|------------|-------------------------|
| No HTN Medications               | 4.98       | 2.25 – 11.02            |
| Currently taking HTN Medications | 1.95       | 1.20 – 3.16             |
| Hypertension and < 55 yrs        | 7.68       | 2.65 – 22.5             |
| Hypertension and current smoker  | 6.12       | 2.29 – 16.35            |

*Adapted from Gorelick, 1999*

### 15.1.7.2 Age and Race

The incidence of hemorrhagic stroke increases with age. Dyken (1984) reported that the risk of developing stroke increases with increased age, and doubles with every decade after 55 years of age. While age is a major risk factor, in general, people with stroke are likely to have more than one risk factor. Risk of hemorrhagic stroke is also increased in certain races, e.g., African Americans. Incidence rates from the incidence-prevalence database IRIS/CASES (status of 2000) are presented in Table 52, which demonstrates an increase in intracerebral hemorrhage with increasing age and an increase in African Americans (men and women) compared with those reported for Whites, which level off at the 75-84 and  $\geq 85$  age groups.

**Table 52: Published Incidence Rates for Intracerebral Hemorrhage from the Incidence and Prevalence Database IRIS/CASIS**

| Age Category (years) | Men   |       | Women |       |
|----------------------|-------|-------|-------|-------|
|                      | White | Black | White | Black |
| 0-44                 | 2     | 8     | 2     | 7     |
| 45-54                | 10    | 36    | 9     | 33    |
| 55-64                | 27    | 101   | 24    | 92    |
| 65-74                | 71    | 129   | 65    | 116   |
| 75-84                | 148   | 148   | 134   | 134   |
| ≥85                  | 154   | 154   | 139   | 139   |

In the large Stroke Prevention in Atrial Fibrillation II trial (1994), differences associated with an increase in incidence of intracranial hemorrhage were seen in the older participants. The rate of intracranial hemorrhage with ASA use was 0.8% per year in patients older than 75 years of age vs. 0.2% per year in patients 75 years of age and younger.

#### 15.1.7.3 Amyloid Accumulation

Stroke can be caused by the accumulation of amyloid within the artery walls, particularly in the elderly. This makes the arteries more prone to bleeding. The pathology of cerebral hemorrhage in ASA users may be different to that of spontaneous intracerebral hemorrhage caused by chronic hypertension. Cerebral hemorrhage often affects lobar areas, while spontaneous intracerebral hemorrhage affects the basal ganglia (Wong et al., 2000). The investigators commented that the predominance of ASA induced hemorrhages in the lobar areas suggests the presence of a vascular abnormality such as amyloid angiopathy, which is known to affect older patients. MRI follow-up in a subgroup of patients showed the presence of microbleeds at sites other than that of the primary intracerebral hemorrhage.

#### 15.1.7.4 Epistaxis

A history of epistaxis while receiving high-dose ASA (>1,225 mg/week) has been identified as an independent risk factor for hemorrhagic stroke. Saloheimo (2001) and colleagues evaluated 98 patients with primary intracerebral hemorrhage between the ages of 36 and 90 years of age. Their findings demonstrated that epistaxis might increase risk of intracerebral hemorrhage in subjects using ASA. (OR of epistaxis, 2.75, 1.11–6.81; OR of ASA use, 14.7, 2.03-106). In addition, there was a significant positive interaction between the history of epistaxis and the use of ASA on the risk for intracerebral hemorrhage.

#### 15.1.7.5 Dose

Thrift and colleagues (1999) evaluated the relationship between the use of ASA or other NSAIDs and the risk for hemorrhagic stroke. They reported that the use of low-dose ASA (<1,225 mg/week) was not associated with an increased risk for hemorrhagic stroke with an odds ratio of 1.00 (CI=0.06-1.66) in multivariate risk-adjusted analyses. Larger doses of ASA were associated with hemorrhagic stroke with an odds ratio of 3.05 (CI=1.02-9.14).

#### 15.1.7.6 Other Risk Factors

Patients with aneurysms are at an increased risk of developing intracerebral hemorrhage in general and use of ASA may potentiate this risk (De La Monte et al., 1985). Other independent risk factors included previous ischemic stroke, epilepsy, or strenuous physical exertion (Saloheimo et al., 2001).

#### 15.1.8 Conclusion

ASA is a valuable and cost effective antiplatelet agent, with an excellent benefit-risk profile in both the secondary and primary prevention indications. Antiplatelet therapy is associated with an increased risk of bleeding, although low-dose ASA is associated with the lowest risk of bleeding among the antiplatelet agents. As intra- and extra-cranial hemorrhage risk associated with ASA 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 ASA is used for secondary prevention, the benefit from ASA clearly outweighs possible harm from a major hemorrhage. In primary prevention, the balance between benefit and harm is equally clear for patients where the CHD risk is at least moderate. Furthermore, the benefit-risk relationship can be enhanced by greater education and research regarding hemorrhagic stroke and its causes. Likewise, efforts to control blood pressure will have a significant 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 ASA therapy in primary prevention patients being 0.2 events per 1,000 patient-years. That is, for every 1,000 patients treated for a 5-year period, ASA therapy would be expected to result in 1 excess hemorrhagic stroke. Overviews of secondary and primary prevention trials suggest a comparable increased risk of about 1 or 2 per 1,000 patients.

Based on the rarity of hemorrhagic stroke risk associated with the use of low-dose ASA, it is clear that many more heart attacks can be prevented with relatively low increases in adverse hemorrhagic events with appropriate patient selection. As such, it is important that the rare risk of hemorrhagic stroke not interfere with broader access to this important therapy that has the potential to dramatically reduce the burden of MI.