



**Integrated Summary
of Safety**



VOLUME 3

13 INTEGRATED SUMMARY OF SAFETY

13.1 General Overview of ASA Safety Profile

ASA has been marketed for more than 100 years and is one of the most extensively studied drugs, thus its adverse event profile is well understood. The initial safety profile was established largely from experience with analgesic and anti-inflammatory use. Through numerous controlled clinical trials and tens of millions of patients exposed each year for cardiovascular indications, a clear picture regarding the potential risks associated with chronic ASA therapy has been developed.

Several factors distinguish the use of ASA in cardiovascular prevention from its use for analgesic and anti-inflammatory indications. Cardiovascular dosing is typically lower and the duration of use is long-term rather than episodic. In addition, patients at risk for cardiovascular events are more likely to have underlying disease (e.g., diabetes mellitus, hypertension, and hyperlipidemia) and to be using other medications. For these reasons, the large, controlled clinical trials evaluating ASA for the prevention of cardiovascular events (i.e., the primary and secondary prevention trials) and the extensive post-marketing experience for cardiovascular event prophylaxis should be considered in evaluating the potential risks of low-dose ASA treatment.

13.1.1 Mechanism of Action Relationship to Safety

Clinically relevant hazards of ASA (bleeding) are related to the mechanism of action underlying its therapeutic utility. The mechanism of action of ASA has both a beneficial (see Section 11) and a safety-related impact that is affected by dose and duration. Inhibition of prostaglandin synthesis by ASA has been implicated in its tendency to cause GI adverse reactions (Stiehl, 2000), including, in rare cases, gastric perforations, ulcers and bleeding. This effect is largely due to the inhibitory effects on a gastroprotective substance. In addition, as a result of its acidic nature, ASA can have direct effects on the gastric mucosa. In the highly acidic environment of the stomach, ASA is non-ionized and able to migrate across cell membranes into the superficial epithelium where it traps hydrogen ions. This can attenuate the protective effects of gastric mucosa, leading to epithelial damage (Green, 2001).

Through its inhibitory role in thromboxane synthesis, and its subsequent inhibitor effects on platelet aggregation, ASA has been associated with the rare but unwanted side effect of increasing the risk of bleeding from a variety of other sites as well. The most concerning relates to the risk of intracerebral hemorrhage (i.e., hemorrhagic stroke).

Under certain conditions, renal blood flow is prostaglandin mediated, and thus can be affected by ASA use. As a result, patients with underlying renal disease or those on diuretics should use ASA with caution. Because this affect of ASA is known, however, it can clearly be handled through appropriate labeling.

13.1.2 Adverse Events – Relationship to Dose and Duration of Therapy

The adverse events reported for ASA are, for the most part, non-serious and extremely rare at low doses. As is the case for most drugs, adverse events associated with the use of ASA are dose and duration dependent. With short-term, episodic, OTC labeled use, the rate of adverse events does not significantly differ from other OTC analgesics, including acetaminophen. In fact, a retrospective meta-analysis of 3,700 patients in 54 single-dose ASA (325-1300 mg) dental pain studies found that occurrences of adverse events did not differ from placebo (Cooper and Press, 1985). When large doses are administered, including overdose situations, or when it is given for sustained periods, the incidence of unwanted effects increases.

13.1.3 Types of Adverse Events Associated with ASA

Gastrointestinal adverse effects are by far the most commonly reported complaint with ASA therapy. Adverse effects include abdominal pain, heartburn, nausea, vomiting, and in some cases, gastro-duodenal ulcer and perforation. These events are generally dose related and less of a concern with low-dose ASA (75-325 mg/day).

A less common event associated with ASA is the occurrence of intracranial bleeding, or hemorrhagic stroke. This is a very rare event and typically associated with higher doses or in patients with other risk factors, but the seriousness of such an event is significant with regard to outcome. Renal adverse effects have also been associated with ASA therapy, although this is generally associated with patients taking high doses of ASA.

Other precautions/adverse events associated with ASA are generally related to overdose, (e.g., central nervous symptoms), allergy, drug-drug interactions and contraindications. These symptoms rapidly disappear once the dosage is reduced. Tinnitus and hearing loss are dose related and are considered to be the first signs of chronic salicylate intoxication. Hypersensitivity reactions resulting in rashes and asthma reactions, and more severely, anaphylaxis have been reported.

13.1.4 Concomitant Therapy and Contradictions Impacting Adverse Event Profile

As the mechanism of action is implicated in the adverse event profile of ASA, e.g., prostaglandin inhibition and antiplatelet effects, it is not surprising, that the risk of bleeding is enhanced with concomitant use of ASA with anticoagulants and other NSAIDs. Therefore, ASA labeling cautions against use with these medications unless recommended to do so by a physician. Other potential interactions include high-dose ASA with diuretics and angiotensin converting enzyme (ACE) inhibitors leading to decreased renal prostaglandin synthesis and a subsequent decrease in glomerular filtration. The interaction of high-dose ASA and ACE inhibitors leading to a reduction in the antihypertensive effect has been reported, although recent studies have demonstrated that the use of ACE inhibitors and ASA is beneficial. Loer et al (1999) evaluated 11,575 patients with coronary artery disease, 1,247 (11%) of these patients were treated with

ACE inhibitors, of which 618 (50%) used ASA. The patients treated with ACE inhibitors and ASA were associated with lower mortality than treatment without ASA. This was again demonstrated in a study (Krumholz et al., 2001) evaluating 14,129 post-MI patients, where 26% received ASA only, 20% received ACE inhibitors only, 38% received both, and 16% received neither. Prescribing both ASA and ACE inhibitors was associated with a slightly lower risk (non-significant) of mortality that was seen in ASA-only or ACE inhibitor-only group. Thus the therapeutic attributes of low-dose ASA for the reduction of CV events for those on ACE inhibitor should be considered by the physician since this interaction is limited to high (non-CV) doses of ASA. High doses of ASA have also been associated with an increased hypoglycemic effect with antidiabetics via its own hypoglycemic action.

Contraindications for ASA use include active peptic ulcers, hemorrhagic diathesis, hypersensitivity to ASA or other salicylates, a history of asthma induced by the administration of salicylates or substances with a similar action (e.g., NSAIDs), combination with methotrexate at doses of 15 mg/week or more, and the last trimester of pregnancy. Precaution should be used during concomitant treatment with anticoagulants, in patients with a history of gastro-intestinal ulcer/bleeding, impaired renal function and impaired hepatic function.

13.1.5 Summary

Based on the large number of trials involving many thousands of patients exposed to ASA for long periods of time for the prevention of cardiovascular events, much is known about the risk of ASA when used for the proposed indication. In fact, controlled clinical evaluation data for up to 7 years of treatment is available, providing a clear indication of the risks associated with the treatment across a wide range of patients with a variety of co-morbid conditions and drug use. In these clinical trials, the most important serious adverse events associated with ASA are GI and intracerebral hemorrhage, which occur at relatively low rates and typically occur in those at higher risk. Thus, appropriate labeling can address these concerns.

Based on the totality of the cardiovascular use evidence, it is reasonable to estimate that for every 1,000 patients treated, ASA therapy would be expected to cause on average 1 significant extracranial bleeds and for every 10,000 patients treated and 1 case of hemorrhagic stroke while preventing 14 MIs. Clear labeling that encourages a comprehensive assessment of risk factors for hemorrhage would be expected to lower these rates appreciably.

13.2 Safety by Body System

The evidence supporting the safety of ASA for the intended use is reviewed in the sections below, with an emphasis on GI effects and intracerebral effects. Renal effects, although not considered to be as significant, are also reviewed.

13.2.1 Gastrointestinal Effects

A detailed review of gastrointestinal safety of ASA is included in Attachment 1.

13.2.1.1 Overview

It is widely recognized that the most common health risk of long-term ASA use is bleeding caused by the same mechanism that is responsible for ASA's cardiovascular benefits: inhibition of prostaglandin synthesis. While the most serious and life-threatening manifestation of an increased risk of bleeding is intracerebral hemorrhage, gastrointestinal bleeding is clearly more prevalent, with serious adverse GI events expected to occur at an annual rate of 1-2% in individuals who take high-dose ASA (or prescription NSAIDs) on a chronic basis for anti-inflammatory benefits (Cryer, 1999).

The risk of GI injury associated with the use of low-dose ASA for cardiovascular protection has been less well-characterized. Nonetheless, data from numerous clinical trials in patients with various cardiovascular disease manifestations, as well as those from apparently healthy individuals administered ASA in the primary prevention studies, provides significant insight regarding expected rates of adverse events. These data coupled with the extensive marketing experience with ASA provide certainty regarding the risks associated with the proposed broadening of the labeling to include patients at moderate CHD risk or greater who have not experienced a previous cardiovascular event.

Since data on the gastrointestinal side effects of low-dose ASA (≤ 325 mg/day) used chronically are relevant, regardless as to whether the use was to prevent a first or subsequent cardiovascular event, evidence from all long-term studies are reviewed. Recently published data (e.g., Topol et al., 2003; Peters et al., 2003) that have not been described in earlier submissions or review articles dealing with GI toxicity are also incorporated into this evaluation bringing this review up to date. In addition, in order to provide an understanding of the real world uses of ASA, post-marketing surveillance data is also reviewed, including an unpublished analysis of spontaneous report data currently on file with FDA. Finally, because a great deal of knowledge has accumulated pertaining to the specific factors that are known to influence GI toxicity (e.g., ASA dose, formulation, duration of exposure, age, concomitant drug use, and previous history of GI events), these data are also reviewed with the expectation that they will help to enhance labeling to minimize the risk of ASA exposure in the proposed new indication.

Through a synthesis of these data sets, it is possible to rigorously weigh ASA's benefits against its GI risks to come to a well-considered and meaningful benefit-risk analysis for low and moderate-risk patient populations that take into account all of the available data. Taken together, the totality of the data provides reassuring information supporting the view that the GI risks of ASA are readily quantifiable, and that these risks are outweighed by ASA's robust cardiovascular benefits, even in lower risk populations when patients are appropriately selected based on a comprehensive cardiovascular risk assessment.

13.2.1.2 Overview of Gastrointestinal Effects from the Primary Prevention Trials

Data relevant to the GI side effects of ASA derived from the 5 primary prevention trials are summarized in Table 21. The most striking aspect of these data, when looked at in totality, is that while ASA increased the rate of gastrointestinal hemorrhage in all of the 5 primary prevention trials, the absolute rates were extremely low. The total number of fatal GI bleeding events across the studies was 9 in the ASA group and 7 in the control group. Furthermore, while the estimates varied slightly across trials (Isles et al., 1999), the data are remarkably consistent, resulting in estimates ranging from 0.4 to 1.7 excess bleeds per 1,000 patients treated. This aggregation of data provides a high level of confidence that the risk of GI adverse events in patients at low to moderate baseline risk of cardiovascular events is low and predictable.

Table 21: Major GI Events in Primary Prevention Trials

Trial	Type of Gastrointestinal Bleeding	Cumulative Incidence		P Value	Excess Bleeding Events per 1000 Patients Treated per Year	Fatal Gastrointestinal Bleeding Events	
		ASA Group	Control Group			ASA Group	Control Group
		%				N	
BDT	Self-reported peptic ulcer disease	2.6	1.6	<0.05	1.7	3	3
PHS	Upper gastrointestinal ulcers	1.5	1.3	0.08	0.4	1	0
TPT	Major or intermediate bleeding†	1.7	0.8	NR	1.3	0	1
HOT	Fatal and nonfatal major gastrointestinal bleeding events‡	0.8	0.4	NR	1.1	5	3
PPP	Gastrointestinal bleeding§	0.8	0.2	NR	1.5	0	0

Adapted from Hayden, 2002

*BDT = British Male Doctors' Trial; HOT= Hypertension Optimal Treatment Trial; PHS = Physicians Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial; NR = not reported

†Major bleeding included fatal and life-threatening hemorrhages that required transfusion, surgery, or both. Intermediate episodes were bleeding events that prompted patients to notify research coordinators separately from routine questionnaires

‡Major bleeding was not defined.

§Described as severe but nonfatal

To better estimate the potential risks of ASA treatment in the primary prevention setting, a number of meta-analyses have been conducted which integrate the data from these 5

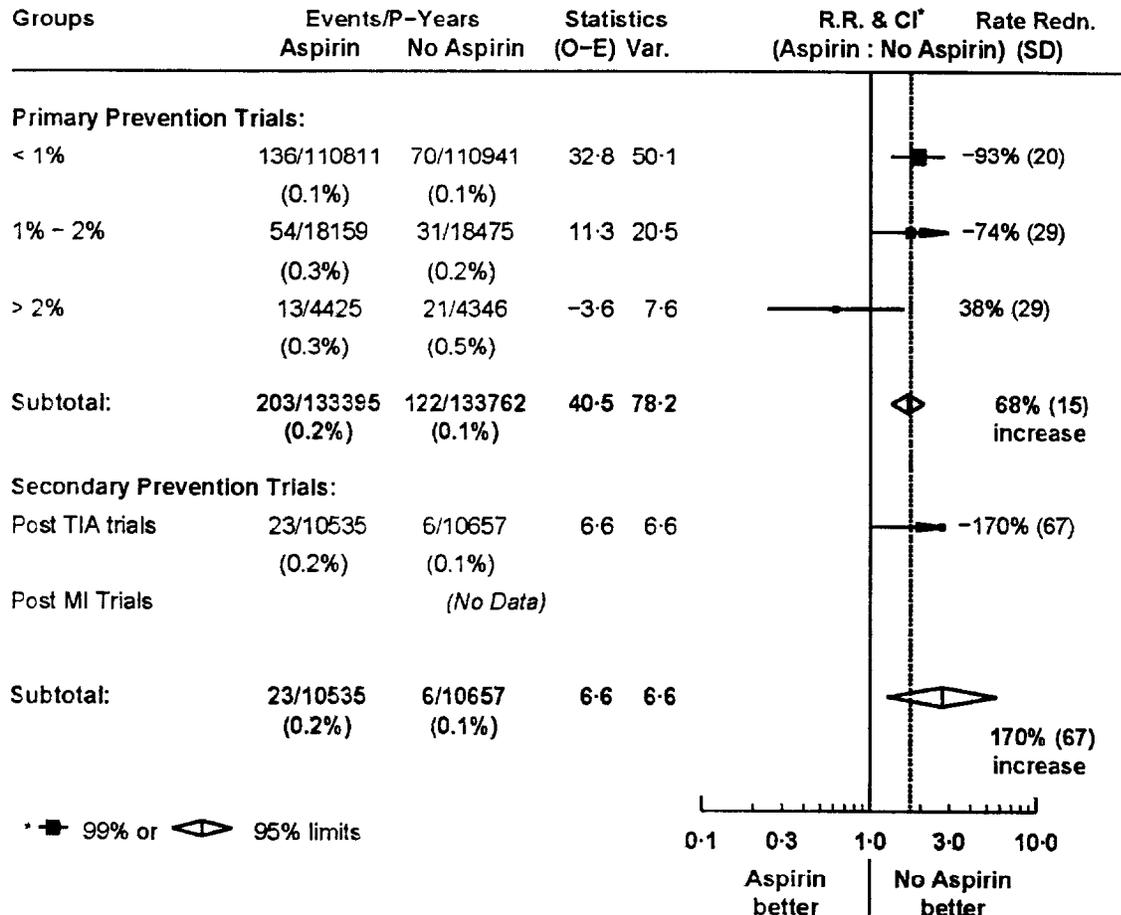
studies to draw conclusions about the overall safety of ASA. Based on the relative paucity of events reported, such meta-analyses provide relevant insight on the potential for GI complications, and thus are discussed below.

The USPSTF meta-analysis conducted by Hayden and colleagues (2002) considered all 5 primary prevention studies to evaluate the risk of gastrointestinal bleeding. An odds ratio for ASA therapy was estimated to be 1.7 (CI=1.4-2.1), or an excess risk for major (mostly gastrointestinal) bleeding events of 0.7 (CI=0.4-0.9) per 1,000 patient-years. As would be expected, this estimate falls right in the middle of the estimates for each of the individual trials (discussed above). Sudlow (2001, cited in Guise, 2002) pooled the data on major extracranial bleeding from the 5 primary prevention trials and reported essentially identical results.

Finally, the Antithrombotic Trialists' Collaboration Primary Prevention Group recently conducted a comprehensive meta-analysis based on individual patient data from the 5 available low-risk primary prevention trials (FDA AC Presentation, December 8, 2003) and specifically analyzed the risks of ASA therapy across these studies which were presented to the Cardiovascular & Renal Drugs Advisory Committee on December 8, 2003. A more detailed analysis and commentary of these data are expected to be available to the agency shortly. Their conclusion was that low-dose ASA use is associated with a small, but clinically important increase in the risk of extracranial bleeding. In their analysis, there were a total of 203 such events in the ASA group compared to 122 in the non-ASA group, corresponding to a non-statistically significant 68% increase. It is important to note that this small number of events must be compared to the significant exposure of over 130,000 patient-years in each group. This comparison highlights an absolute risk of extracranial bleeding of 0.2% in the ASA group compared to 0.1% in the placebo group (Figure 16). Importantly the risk of extracranial bleeding was not influenced by baseline CHD risk. These findings do not differ significantly to analyses from secondary prevention studies.

From their analysis, is estimated that ASA use might cause 4 - 5 major extracranial bleeds per 1,000 patients treated for 5 years. (See Figure 17)

Figure 16: ATT Primary Prevention – Effects on Major Extracranial Bleeds



Test for heterogeneity between subtotals: $\chi^2_1 = 1.4$; $P = 0.2$; NS

Adapted from FDA AC Presentation, December 8, 2003

Figure 17: Events Avoided or Caused per 1,000 Individuals Treated with ASA for 5 Years

Annual risk of CHD event	Avoided		Caused	
	CHD event	Ischemic stroke	Hemorrhagic stroke	Major bleed
<10%	5	0	1	5
10-20%	14	0	1	5
Secondary	25-50	25-50	1	5

Adapted from FDA AC Presentation, December 8, 2003

13.2.1.3 Post-Marketing Experience of Gastrointestinal Effects

Based upon the vast amount of clinical trial data summarized above, the rate of GI adverse effects appears to be well-established, consistently low, and independent of whether individuals had a previous cardiovascular event to qualify for entry. However, clinical trial studies have strict inclusion and exclusion criteria that limit their ability to be predictive of the real-world experience. In the case of ASA, the real world use experience is substantial, with over 22 million Americans exposed to low-dose ASA on a chronic basis for cardiovascular disease management. As such, post-marketing surveillance and risk assessment programs can be useful in helping to identify adverse event trends that may not be elucidated by clinical studies and meta-analyses and therefore could be used to provide added confidence around the risk estimate.

The interpretation and usefulness of spontaneous adverse event report data in assessing risk is however, 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 report, including the association of the event and drug, among others. Therefore, it is important to note this type of information should only be used to confirm rates reported in more controlled situations, or to identify trends, and should not be used to by themselves to establish true incidence rates.

An analysis of spontaneous upper GI perforations and bleeding cases (referred to as upper GI events or cases) associated with ASA use was conducted (Bayer HealthCare, 2003). The objective of the analysis was to evaluate the rate of upper GI events for spontaneous cases reporting ASA at doses less than or equal to 100 mg/day compared with cases mentioning doses greater than 100 mg/day. The analysis also sought to evaluate the risk factors associated with an increase in risk of upper GI events and therefore included all reports of adverse event cases treated with ASA with known indications (antiplatelet or analgesic use) through December 2, 2003. Cases that reported ASA overdose or exceeded the recommended dose were excluded. The MedDRA reference terms were used to identify upper gastrointestinal bleeding and perforation cases.

A total of 1,976 adverse event reports associated with ASA doses of less than or equal to 100 mg/day, and 4,091 AE reports associated with ASA at doses greater than 100 mg/day

were identified. Of these cases, 66 cases treated with a dose less than or equal to 100 mg/day, and 383 cases treated with doses > 100 mg/day were excluded from the analysis due to exceeding the recommended dose, leaving 1,910 and 3,708 cases in the two groups respectively. The indication was unknown for 52 cases in the higher dose group (>100 mg/day), resulting in their exclusion from the analysis. Of the total adverse event reports, upper GI cases represented 956 cases, 433 for \leq 100 mg and 523 for the > 100 mg dose group.

When reporting rates are evaluated in relationship to sales volume, patient exposure days can be converted into patient exposure in patient-years (py) (by dividing by 365.25). As shown in Table 22, the reporting rates are higher for ASA doses greater than 100 mg/day than for ASA doses less than or equal to 100 mg/day regardless of the intended use.

Table 22: Worldwide Reporting Rates of Upper GI Cases Based on Patient Exposure as Derived from Sales Data

	ASA \leq 100 mg		ASA > 100 mg	
	No. Cases/py	No. Cases/10 ⁶ py	No. Cases/py	No Cases/10 ⁶ py
Antiplatelet Use	315 / 124.61*10 ⁶	2.5	210 / 43.25*10 ⁶	4.9
Pain Use	118 / 124.61*10 ⁶	0.9	313 / 43.25*10 ⁶	7.2
Combined	433 / 124.61*10 ⁶	3.5	523 / 43.25*10 ⁶	12.1

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

Results of the analysis demonstrate that of the upper GI cases associated with antiplatelet use, 60% (315/525) were associated with ASA doses of \leq 100 mg/day and 40% (210/525) with doses > 100 mg/day. For those cases associated with analgesic use, 27.4% (118/431) of cases were associated with the low-dose and 72.6% (313/431) with the higher dose.

Table 23: ASA Spontaneous Reports Distribution by Indication

Population	Indication	ASA ≤ 100 mg	ASA > 100 mg
All Cases	Antiplatelet use	1,229 / 1,910 (64.3%)	847 / 3,708 (22.8%)
	Analgesic use	681 / 1,910 (35.7%)	2,407 / 3,708 (64.9%)
	Unknown		454 / 3,708 (12.2%)
Cases with upper GI events	Antiplatelet use	315 / 433 (72.7%)	210 / 575 (36.5%)
	Analgesic use	118 / 433 (32.3%)	313 / 575 (54.4%)
	Unknown		52 / 575 (9.0%)

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. Likewise, the median age of the cases with upper GI events is higher than those with other events (Table 24), however, there is nearly no difference in the median age between cases with known risk factors and without known risk factors in both groups of cases (Table 25).

Table 24: Age Distribution by Indication

Population	Indication	ASA ≤ 100 mg	ASA > 100 mg
All Cases	Antiplatelet use	72 years	70 years
	Analgesic use	69 years	54 years
Cases with upper GI events	Antiplatelet use	75 years	73 years
	Analgesic use	72 years	64 years

Bayer HealthCare, Data on File, 2003

Table 25: Age Distribution for Different Risk Groups

	Indication	ASA ≤ 100 mg (n)	ASA > 100 mg (n)
Cases with upper GI events and known risk factors	Antiplatelet use	75.0 years (164)	71.5 years (72)
	Analgesic use	72.0 years (55)	65.0 years (115)
Cases with upper GI events and without known risk factors	Antiplatelet use	75.5 years (138)	73.5 years (124)
	Analgesic use	73.0 years (55)	62.5 years (188)

Bayer HealthCare, Data on File, 2003

The proportion of cases with upper GI events was higher in those cases with a known risk factor. The risk factors included concomitant drug use (NSAIDs, antithrombotics, corticosteroids or ginkgo) and/or underlying diseases (gastric ulcer disease, *H. pylori*, or other disease-causing GI bleeds), and smoking and alcohol use. Results of the analysis for the combined indications demonstrated that from those cases treated with doses \leq 100 mg/day, 53.1% of those cases with upper GI events (230/433) presented with risk factor(s) vs. 46.9% without a risk factor. The cases treated with doses $>$ 100 mg/day demonstrated that 36.7% of those cases with upper GI events (192/523) presented with risk factor(s) vs. 63.3% without a risk factor (Table 26). When age is also considered a risk factor ($>$ 75 years), the proportion of upper GI cases that occurred without any risk factor is reduced from 46.9% (excluding age) to 24.7% in the lower dose groups.

Table 26: Risk Factor Summary – Antiplatelet and Pain Indications*

	ASA \leq 100 mg		ASA $>$ 100 mg	
	Cases with Upper GI events (n=433)		Cases with upper GI events (n=523)	
With any risk factor	230	53.1%	192	36.7%
Without any risk factor	203	46.9%	331	63.3%

Bayer HealthCare, Data on File, 2003

* Risk factors included concomitant medications, underlying disease that cause bleeding, smoking and alcohol

This analysis supports findings from previous post-market surveillance studies (Gessner and Latta, 1999; Karwoski, 2002) – specifically that GI adverse event rates associated with the real world use of ASA are consistent with the findings of controlled clinical trials and that individuals with one or more risk factors are at an increase risk of developing an upper GI event, suggesting that physician and patient education could modify the risk (See Attachment 1 for discussion of GI risk factors)

13.2.1.4 Conclusion - Risk of Gastrointestinal Effects

Based upon on the consistent results from hundreds of rigorously controlled clinical trials that have evaluated the long-term use of low-dose ASA, it is clear that rate of adverse GI effects associated with ASA is low and ranges from 0.4 to 1.7 excess major bleeding events per thousand patients treated. The rate of GI events in the 5 primary prevention studies, not surprisingly, does not differ from the estimate demonstrated by the larger ASA database, suggesting that patients at low or moderate baseline cardiovascular risk do not differ from high-risk (secondary prevention) patients with respect to their risk of GI injury. The likelihood of GI toxicity appears to be influenced by dose, but only at doses at the upper end of the dose spectrum (i.e., above 325 mg/day), but not within the low-dose range (i.e., 75 mg – 325 mg). There are conflicting data and/or debate as to whether GI toxicity is influenced by formulation (i.e., enteric coated or uncoated), duration of use, increased age, and existence of previous GI complications. There is however, growing

support for the view that concomitant use of other NSAIDs (including COX-2 inhibitors) increases the risk of GI toxicity with ASA.

Considering the totality of the data, the medical benefits of properly managed low-dose ASA treatment for cardiovascular disease has been shown to outweigh the risks of gastrointestinal complications in individuals at moderate and high baseline risk for adverse cardiovascular events (Fries et al., 1993; Weisman and Graham, 2002). Consistent with this view, the benefit-risk profile of ASA has been clearly set forth by the U.S. Prevention Services Task Force and the American Heart Association (USPSTF, 2002; Pearson et al., 2002) where they documented that the cardiovascular benefits outweighed the risks of adverse GI effects in patient populations at low-moderate (6% baseline 10-year risk) and moderate ($\geq 10\%$ baseline 10-year risk) risk for experiencing a CHD event over a five year period. Based on the above-mentioned evidence, it is clear that at least 14 nonfatal MIs can be prevented for every 2-4 GI bleeds caused. As the consequences of an MI are of greater significance than a GI bleed, more widespread use of ASA in this population is warranted.

13.2.2 Intracranial Bleeding (Hemorrhagic Stroke)

A detailed review of hemorrhagic stroke is included in Attachment 2.

13.2.2.1 Overview

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. The most serious risk associated with the use of ASA is the potential increased risk of intra- and intercranial bleeding, or hemorrhagic stroke (ISIS-2, 1988; UK-TIA Study Group, 1991; Juul-Møller 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 increased 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.

Recent meta-analyses confirm that the risk of hemorrhagic stroke is extremely low. Nonetheless, 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. 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 has been provided in Attachment 2.

13.2.2.2 Overview of Intracranial Bleeding from the 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 27.

Table 27: 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 (0.21%)	12/11,034 (0.11%)	1.92 (0.95 – 3.86)	0.20
BDT	13/3,429 (0.38%)	6/1,710 (0.35)	1.08 (0.41 – 2.85)	0.05
TPT	3/1,268 (0.24%)	2/1,272* (0.16%)	1.51 (0.25 – 9.03)	0.12
HOT	14/9,399 (0.15%)	15/9,391 (0.16%)	0.93 (0.45 – 1.93)	(0.03)
PPP	2/2,226 (0.08%)	3/2,269 (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, NR=Not Reported

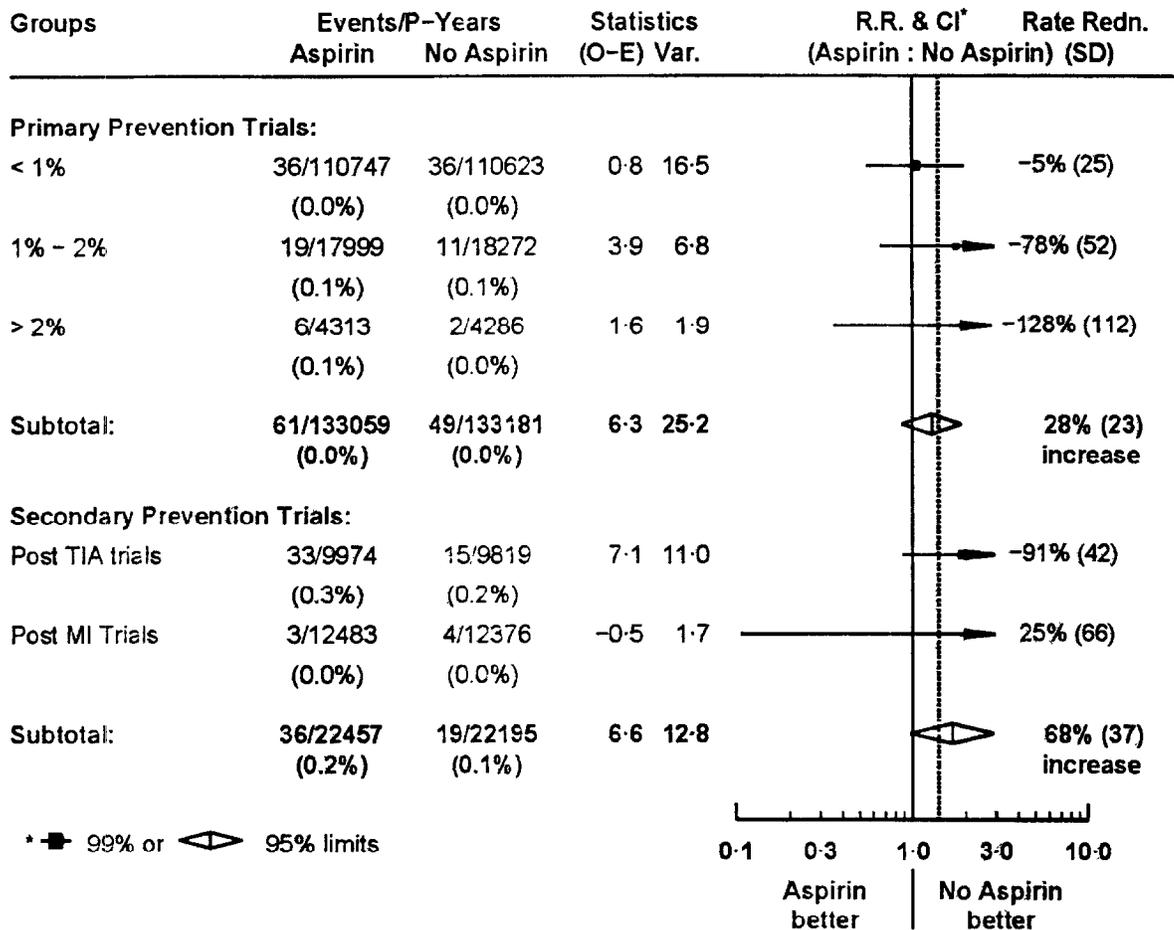
* Data from patients who received warfarin are not included

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 Antithrombotic Trialists' Primary Prevention Subgroup analyzed the risks of ASA as it relates to hemorrhagic stroke. The hemorrhagic stroke findings are similar to those observed with other bleeding events, although significantly less common in occurrence. In this analysis, 61 cases of presumed hemorrhagic stroke were recorded for the ASA group compared to 49 in the non-ASA group, translating to an absolute rate of 0% in both groups which is consistent with a non-significant 28% increase in risk with ASA. Similarly, secondary prevention analyses have shown a non-significant trend in favor of increased risk with ASA (Figure 18).

Nonetheless, these findings taken together demonstrate the rarity of the occurrence of hemorrhagic stroke.

Figure 18: ATT Primary Prevention – Effects on Definite Hemorrhagic Stroke



Test for heterogeneity between subtotals: $\chi^2_1 = 0.6$; $P = 0.4$; NS

Adapted from FDA AC Presentation, December 8, 2003

13.2.2.3 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 as discussed previously. As such, 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 at doses ≤ 100 mg/day compared with cases treated with ASA at doses > 100 mg/day 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 at doses ≤ 100 mg/day and 4,091 E reports associated with ASA at doses > 100 mg/day were identified. Of these cases, 66 cases treated with ASA ≤ 100 mg/day and 383 cases treated with ASA > 100 mg/day were excluded from the analysis due to exceeding the recommended dose, leaving 1,910 cases treated with ASA ≤ 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 28, the reporting rates calculated worldwide are much lower than those given in the incidence-prevalence database (IRIS/CASIS, 3/20/2000).

Table 28: Worldwide Reporting Rates of Hemorrhagic Stroke Cases Based on Patient Exposure as Derived from Sales Data

	ASA ≤ 100 mg		ASA > 10 mg	
	No. Cases/py	No. Cases/10 ⁷ py	No. Cases/py	No Cases/10 ⁷ py
Antiplatelet Use	23 / 12.461*10 ⁷	2	22 / 4.325*10 ⁷	5
Pain Use	15 / 12.461*10 ⁷	1	9 / 4.325*10 ⁷	2
Both Indications	38 / 12.461*10 ⁷	3	31 / 4.325*10 ⁷	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 ≤ 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 ≤ 100 mg and 0.4% (9/2,398) of cases treated with ASA > 100 mg reported cerebral bleeding cases.

Table 29: ASA Spontaneous Reports Distribution

Population	Indication	ASA ≤ 100 mg	ASA > 100 mg
All Cases	Antiplatelet use	1,229 / 1,910 (64.3%)	819 / 3,708 (22.1%)
	Analgesic use	681 / 1,910 (35.7%)	2,398 / 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 ASA 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.

13.2.2.4 Conclusion - Risk of Hemorrhagic Stroke

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.

In addition, the post-marketing surveillance evaluation did not show an increased reporting of cerebral bleeding events for ASA. 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 in Attachment 2, should prove helpful in developing labeling to guide physicians and patients regarding the risk of hemorrhagic stroke in the primary prevention population.

13.2.3 Renal Effects

13.2.3.1 Overview

Inhibition of COX and the production of prostaglandins by ASA can have an impact on renal function since maintenance of normal renal function has been shown to be partly dependent on intact renal prostaglandin synthesis. Renal prostaglandins have been shown to be involved in the release of renin, local vascular tone, sodium and water homeostasis, and potassium balance and are increased in response to stress, such as that seen with decreased renal blood flow or blood volume (Whelton and Hamilton, 1991). Furthermore, evidence suggests renal function can be adversely affected in certain high-risk individuals with underlying renal disease (Dunn and Zambraski 1980; Dunn et al., 1984).

13.2.3.2 Renal Effects of ASA

ASA has been reported to be a less potent blocker of COX and production of prostaglandins than the other NSAIDs (Vane, 1971), thus the potential risk of renal toxicity associated with ASA, especially with low-dose ASA, would be expected to be low. In fact, in clinical studies of long-term ASA ingestion that have controlled for concomitant use of analgesics, have not demonstrated a clinically significant effect of ASA on the kidneys in patients with normal renal function. Likewise, little effect has been observed in patients with renal insufficiency (Ferguson, 1977; Emkey, 1982).

Renal toxicity has been associated with the analgesics of the NSAID class. The nephrotoxic potential of these analgesics remains controversial as most of the earlier reports of analgesic-associated nephrotoxicity (Spuhler and Zollinger, 1953; Larsen and Moller, 1959; Jacobs and Morris, 1962; Grimlund, 1963; Kincaid-Smith, 1986; Elseviers and De Broe, 1998) which included patients who had taken large amounts of products containing phenacetin, an ingredient that has been taken off the U.S. market due to toxicity.

Clinically it appears that long-term exposure of the kidney to high-dose analgesic combinations often including caffeine presents as chronic, progressive papillary necrosis (Whelton and Hamilton, 1991). While papillary necrosis associated with chronic ASA use alone has been suggested (Krishnaswamy and Nanra, 1976), it is now believed to not be the case as the black pigmentation found within necrotic papillae associated with phenacetin abuse is not seen in patients ingesting ASA alone (Whelton and Hamilton, 1991).

Acute renal failure is generally seen in at-risk individuals with pre-existing reduced renal blood perfusion. The production of vasodilatory prostaglandins in the kidney of these at-risk patients is inhibited by NSAIDs; thus caution should be exercised in recommending NSAIDs, including ASA, to patients with renal abnormalities.

An evaluation undertaken by Bonney and colleagues (1986) comparing incidence of potentially serious drug-related elevations of BUN or serum creatinine among 1,468 patients taking analgesic doses of ASA, ibuprofen and oxaprozin in multi-center clinical

trials demonstrated that all three drugs were associated with a low incidence of significant renal function parameters. Although there were elevations in BUN or serum creatinine levels, there were no serious changes associated with high-dose ASA use (dosages ranged from 2,600 to 3,900 mg daily). Cessation of ASA use typically results in a reversal of drug-induced effects on renal function (Bonney et al., 1986; Whelton et al., 1990).

Long-term, high-dose ASA use in patients with rheumatoid arthritis has been evaluated in a number of studies (Ferguson, 1977, Emkey, 1982) that have failed to demonstrate renal damage. In the study undertaken by Emkey and Mills, 42 patients using ASA continuously for at least 10 years for arthritis had serially measured BUN and creatinine levels taken, and all were within normal limits. End stage renal disease did not develop in any of the patients. In a study by Sandler and colleagues (1989), daily users of ASA were not at significantly higher risk for end stage renal disease than non-users (OR=1.32; CI=0.69–2.51). Perneger and associates (1994) also concluded that frequent ASA use was not associated with an increased risk of end stage renal disease.

A recent report (Caspi, 2003) evaluating kidney function in 83 stable geriatric patients (average 81 years of age) using low-dose ASA (100 mg) for two weeks demonstrated that urinary excretion of creatinine decreased in 72% of the patients and excretion of uric acid decreased in 65% of the patients. The uric acid clearance also decreased. Kidney function improved after ASA dosing was halted.

13.2.3.3 Risk Factors for Adverse Renal Effects

The inhibition of prostaglandin function is more likely to cause complications in at-risk patients with decreased renal blood perfusion than in subjects with normal renal function. The risk of acute renal deterioration is highest in patients with hepatic disease, pre-existing or underlying renal impairment, cardiac failure, protracted volume contraction due to concomitant diuretic therapy or intercurrent disease (e.g., diabetes), or old age (Whelton, 1990; Whelton and Hamilton, 1991). These patients should use caution with non-prescription analgesic self-therapy, especially if using ASA for cardiovascular indications.

13.3 Interactions with Other Analgesics

Concomitant use of ASA with other OTC analgesic ingredients, including the NSAIDs, may increase risk of GI (Garcia Rodriguez, and Hernandez-Diaz, 2001; Rahme et al., 2000) or renal disorders (McEvoy, 2000). The potential increased risk for GI and renal adverse events warrant caution with concomitant use of ASA with ibuprofen, naproxen sodium or ketoprofen.

Importantly, the efficacy of low-dose ASA used for cardiovascular benefit may be compromised by concomitant use of ASA with other NSAIDs. Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardio-protective effects of ASA (Catella-Lawson et al., 2001).

Table 30: Drug-Drug Interactions with ASA that Warrant Caution

Prescription Drug	ASA
Oral Anticoagulants and Heparin	+*
Anti-thrombotics	+
Anti-convulsants	+
Uricosuric Agents	+
Corticosteroids	+
Methotrexate	+**
Certain Sulfonylureas	+***

+ = Drug-drug interaction requires caution due to inherent risk of adverse event

*Despite the interaction between ASA and heparin use, the American College of Cardiology and AHA promote the use of ASA and heparin for management of patients with acute coronary syndrome (unstable angina) (Ryan et al., 1999)

**ASA administration to patients receiving low-dose methotrexate therapy for treatment of rheumatic conditions is of little safety concern (Haas, 1999).

***Despite potential interactions between some anti-diabetic drugs and ASA, the American Diabetes Association (ADA) advocates the benefits of ASA, particularly for use as a primary prevention strategy in men and women with diabetes who are at high-risk for cardiovascular events (American Diabetes Association, 2002).

13.4 Post-Marketing Surveillance of ASA

13.4.1 Published ASA Safety Evaluations

It is important to evaluate ASA's safety profile from a post-marketing perspective. A review of reported adverse effects can assist in the development of warnings and contraindications for use, as well as areas for further investigation.

A number of published case analyses have specifically evaluated the GI tolerability of chronic low-dose ASA for cardiovascular prophylaxis and are instructive in assessing the potential hazards of broader ASA use. These analyses are based on findings from observational studies of a variety of types, and hence have differing degrees of reliability. Nonetheless, to provide the reader with a complete understanding of the overall safety picture of ASA they are included herein for completeness.

Three relevant case-control observational studies have been conducted (Weil et al., 1995; Kelly et al., 1996; de Abajo and Garcia Rodriguez, 2001). These three studies specifically evaluated hospitalization for GI bleeding and evaluated the effects of ASA.

Weil and colleagues (1995) evaluated hospitalization for bleeding peptic ulcer with prophylactic ASA regimens of 300 mg or less per day. This case control study was conducted with 1,121 patients presenting with gastric or duodenal ulcer bleeding and age and gender matched hospital and community controls (989 subjects). Prior drug use was assessed by questioning patients who were admitted to selected hospitals in the UK with a report of hematemesis or melena secondary to gastric or duodenal ulcer. Only patients 60 or older were included in this evaluation. The number of cases reporting exposure to

any dose of ASA at any time during the month before admission was 126 compared to 60 for the hospital and 57 for the community controls respectively, resulting in an odds ratio of 4.0 (CI=2.8–5.8). Rates varied appreciably by formulation.

Kelly (1996) evaluated 550 incident cases admitted to 28 Massachusetts hospitals because of acute upper GI bleeding. Cases as well as 1,202 population controls were interviewed regarding their use of ASA and other NSAIDs during the seven days before presenting with a bleed. The odds-ratios for risk of bleeding varied between 2.6 and 3.1 based on various demographic groupings.

The study by de Abajo (2001) represents a retrospective, population-based case control evaluation. Identified incident cases of upper GI bleeding or perforation were from the General Practice Research Database (UK). Controls were randomly selected from the source population. A total of 2,105 cases and 11,500 controls were selected. Among them, 287 (13.6%) cases and 837 (7.3%) controls were exposed to ASA, resulting in a relative risk of 2.0 (CI=1.7-2.3).

13.4.2 Bayer Sponsored Post-Marketing Study

To further evaluate the tolerability of low-dose ASA, Bayer HealthCare conducted an open label post-marketing surveillance study enrolling 2,739 patients recruited from 577 physician practices (Gessner and Latta, 1999). Patients were prescribed 100 mg enteric-coated ASA tablets for prevention of cardiovascular or cerebrovascular events and followed for a period of two years, with 8 visits scheduled over this period. The mean age of participants was 65.4 years (23-97), 40.6% were women, and 57.3% were previously taking another ASA containing product. Interestingly, the main reason many entered the study was because of previous GI complaints (42.2%) or heartburn (19.5%) with previously used ASA formulations.

The mean duration of treatment was 30.2 months. At baseline and at 3-month intervals, patients were evaluated by questionnaire regarding 8 GI symptoms (heartburn, sensation of fullness, GI complaints, nausea, vomiting, constipation, diarrhea, and melena). In addition, bleeding events and other adverse events were collected.

A total of 460 (16.8%) patients did not complete the study. Reasons were lack of compliance, death (not related to study medication), non-medical reasons and others. Only 34 patients (1%) discontinued study medication due to intolerance.

Adverse events were largely (2.3%) non-specific GI complaints (Table 31). GI hemorrhage and gastric ulcer were reported in 0.2% and 0.6% of patients, respectively. Only 10.6% of patients reported at least one adverse event.

Table 31: Adverse Event Rates in Post-Marketing Surveillance Study

Adverse Effect	Patients (n)	Patients (%)	Number of Events	% of Total Number
GI Complaints	64	2.3	68	19.2
Micro-hemorrhage	2	0.1	2	0.6
GI Hemorrhage	6	0.2	6	1.7
Gastric Ulcer	17	0.6	17	4.8
Nausea	5	0.2	5	1.4
Vomiting	2	0.1	2	0.6
Diarrhea	3	0.1	3	0.9
Hypersensitivity Reactions	2	0.1	2	0.6
Other	190	6.9	249	70.3
TOTAL	291	10.6	354	100

Adapted from Gessner and Latta, 1999

13.4.3 FDA Office of Drug Safety Post-Marketing Safety Review

The FDA Office of Drug Safety conducted a review of the post-marketing experience of ASA-containing products relating to GI hemorrhage, ulceration, or perforation to better understand the circumstances that may result in these events. The review was conducted for the NDAC review of OTC analgesics in September 2002. The review was limited to events reported to the FDA from January 1, 1998 through December 31, 2001 (Karwoski, 2002).

The analysis was based on the review of 541 cases of GI hemorrhage, ulceration or perforation reported for ASA-containing products (see Table 32 below). Most reports did not contain complete information related to the patients' prior medical history, medication use, and course of the GI event. The majority of patients in this analysis were taking low-dose ASA (less than or equal to 325 mg per day) for cardio- or cerebrovascular indications. Use for CVD prophylaxis was specifically mentioned in 181 of the cases. Use of multiple preparations containing ASA was reported in only 10 cases (1.9%).

The mean age of patients in this analysis was 69.3 years. For the subset for which gender was reported, 63% (319/503) of the cases were male. The duration of ASA use, while not reported in the majority of the cases, ranged from less than 1 day (after one dose) to 25 years. The median duration for those cases reporting duration was 42 days. The median daily dose and the dose most commonly reported was 325 mg per day.

Eighty six percent of the reports (468) involved hospitalization and 5% (29) died. Medical treatment was indicated in most of the reports, with only 24 patients requiring surgical intervention.

Table 32: Number of GI Events

GI Event or Finding	Number
Bleed	361
Ulceration	197
Perforation	9
Melena	101
Hematemesis	52
Gastritis	29
Hematochezia	20
Erosion	10
Duodenitis	6
Esophagitis	5
Colitis	3
Other GI	4
TOTAL	797

Adapted from Karwoski, 2002

Remarkably, 485 patients (approximately 90%) had one or more risk factors or other possible causes for their GI event. Risk factors included a significant GI medical history (111 cases), concurrent medication that may have increased risk of a GI bleed (366 cases), or a concurrent smoking or drinking history that may have increased risk (75 cases). Sixty-seven percent of the 347 patients listed age greater than 65 as the only risk factor. Additionally, although not quantified, many patients had other significant intercurrent illness or past medical history that might put them at increased risk of a GI event. These findings are suggestive that with appropriate warnings and effective physician evaluation the benefit to risk relationship for ASA can be enhanced.

13.5 Conclusions: ASA Therapy Should Be Recommended for Those Individuals for Whom the Benefit Outweighs the Risk

The safety profile of ASA is well-characterized, toxicity is generally dose-related and adverse events are extremely rare, especially at lower doses. Based upon the data, the most important adverse events due to ASA when used for cardiovascular therapy include the GI effects and intracerebral hemorrhage.

The available data support the following specific guiding principles for arriving at a risk assessment as to whether an individual patient should be considered appropriate for ASA for the prevention of MI:

- The risk of experiencing a first MI increases proportionally with an individual's overall underlying, measurable, cardiovascular risk.
- The appropriateness of any intervention for MI (including ASA therapy) should be evaluated in the context of that individual's global risk of experiencing an MI (first MI or subsequent MI).
- The proportional benefits and risks of ASA therapy are similar in individuals who are at high, moderate, or low-risk and are known and predictable
- Because the proportional risk reductions of ASA are consistent across the studied low-risk and high-risk populations, the benefits can reasonably be expected to extend to a moderate-risk population where the absolute benefits will be greater than the benefits in the low-risk population.
- Controlled clinical evidence supports the conclusion that moderate-risk patients accrue meaningful absolute benefits from ASA therapy that significantly outweigh the risks.
- The benefits of ASA therapy should be offered to those who might accrue the greatest benefit.
- A large number of patients exist who are at sufficiently high-risk of MI to warrant intervention even if they have not had a previous event.
- To maximize the benefit-risk relationship, patients at moderate-risk (e.g., 10% or greater 10-year risk) where the benefit would be expected to far exceed the risk should be specifically included in the labeling.

The approval of ASA use in moderate-risk patients with clear and appropriate labeling will limit exposure to those at sufficiently elevated risk (based on all the available scientific evidence), as well as point out the limitations of the data and, as set forth here, will greatly improve the benefit to risk relationship. Furthermore, such an approach validates the view that decisions are based on the totality of the evidence, including the pathophysiology of the underlying condition. Finally, this approach will restrict access to a more limited population than specifically studied in the pivotal clinical trials.

Based on this recommendation, the routine use of ASA by moderate-risk patients would be expected to result in 14 CHD events prevented at an appropriate level of risk of side effects per 1,000 patients treated in a 5-year period. Based on these findings, ASA represents a worthwhile intervention that should be used more broadly in this population.