

Attachment 1

14 ATTACHMENT 1

14.1 Gastrointestinal Effects

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, its antithrombotic properties. While the most serious and life-threatening manifestation of this side effect is intracerebral hemorrhage, gastrointestinal bleeding is clearly more consistently reported and widespread with serious adverse GI reactions being reported to occur at an annual rate of 1-2% in individuals who take prescription strength NSAIDs and high-dose ASA on a chronic basis (Cryer, 1999).

Data on the gastrointestinal side effects of low-dose ASA (≤ 325 mg/day) when used for the prevention of cardiovascular events in patients across the risk strata and data from trials in individuals who have a history of cardiovascular events and are therefore at higher risk (i.e., the secondary prevention trials) are reviewed. Recently published data (Topol et al., 2003; Peters et al., 2003) that have not been described in earlier review articles dealing with GI toxicity are incorporated into this evaluation bringing this review up to date. In addition, in order to incorporate an understanding from real world uses of ASA, post-marketing surveillance data is also reviewed, including an as yet unpublished analysis of spontaneous reporting data. 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.

Through a synthesis of these data sets, it becomes 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 takes 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 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.

14.2 Overview of Primary Prevention Trials

Data relevant to the GI side effects of ASA derived from the 5 primary prevention trials are summarized in Table 33.

Table 33: 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.

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 groups 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 and moderate baseline risk of cardiovascular events is low and predictable.

A number of meta-analyses have also been conducted which integrate the data from these 5 studies to draw conclusions about the overall effects of ASA for the primary prevention

of cardiovascular disease. For these meta-analyses, the relevant data on GI complications are discussed below.

Hayden and colleagues (2002) conducted a meta-analysis that considered all 5 primary prevention studies and focused on gastrointestinal and cerebral 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. 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). In their analysis, ASA use was associated with a non-statistically significant increased risk of major bleeds (68%), suggesting that ASA might cause 4-5 major extracranial bleeds per 1,000 patients treated for 5 years. These figures are consistent with other analyses. An update of this analysis will be available to the agency shortly.

Thus, based on the totality of the primary prevention database, less than one person in 1,000 would be expected to present with a major GI event in any given year.

14.2.1 Mechanisms of GI Injury

The ability of ASA to produce gastric mucosal damage was first reported using endoscopic methods by Douthwaite and Lintott (1938) and this observation has been corroborated in multiple studies (Sun et al., 1974; Levy, 1974; Silviso et al., 1979). Because the gastric mucosal barrier normally prevents the absorption of hydrogen ions, disruption of this barrier results in back-diffusion of hydrogen ions into the gastric mucosa, which injures cells and damages capillaries and venules. Endoscopically, GI toxicity presents as subepithelial hemorrhages, erosions, and ulcers. Subjective symptoms associated with ASA use have also been reported and include stomach upset, nausea, and constipation. While these effects may appear to be linked, the evidence demonstrates that individuals who experience intolerance are no more likely to experience bleeding complications than those that do not. Likewise, the common observation of endoscopic evidence of a microbleed is not indicative of the potential for more serious outcomes.

ASA induces its gastrototoxicity when the deleterious effect of gastric acid overwhelms the normal defensive properties of the gastric mucosa. This action is the result of both systemic and local mechanisms. The systemic effects include inhibition of the production of prostaglandins which in turn decreases the epithelial mucus, secretion of bicarbonate, mucosal blood flow, epithelial proliferation, and mucosal resistance to injury (Wolfe and Soll, 1999). This effect is achieved through the inhibition of COX, the key enzyme in the conversion of arachidonic acid to prostaglandins (PGs) and thromboxanes (TXs). Of the two isoforms, ASA inhibits both COX-1 and COX-2, but has a more pronounced effect on COX-1. COX-2 plays a role in gastric mucosal defence and ulcer healing, among other roles (DuBois et al., 1998; Warner and Mitchell, 2004; Halter et al.,

2001; Eberhart et al., 1994). COX-1, which is expressed in the GI tract, maintains tissue integrity by generation of PGE₂ and prostacyclin (PGI₂) (Vane and Botting, 1997; DuBois et al., 1998; Warner and Mitchell, 2004). Additionally, COX-1 produces TXA₂ in platelets, which promotes platelet aggregation and thrombi formation. Therefore, by inhibiting COX-1, ASA inhibits PGs and TXA₂ formation, platelet aggregation, and thrombi formation (Vane and Botting, 1997). These actions are largely responsible for ASA's beneficial effect on cardiovascular endpoints (i.e., by preventing formation of thrombi in the vasculature), but also represent the mechanism through which ASA's gastrototoxicity is mediated, suggesting that the benefit and risk cannot be realistically separated.

Local effects on the gastric wall can also be induced by ASA. When ASA is introduced into the acidic medium of the stomach, 90% remains in a nonionized form, resulting in increased gastric absorption (Ivey, 1988) and the potential for topical mucosal effects. ASA also causes topical mucosal damage by diminishing the hydrophobicity of gastric mucus allowing gastric acid and pepsin to injure the surface of the epithelium (Schoen and Vender, 1989), as well as through a series of indirect mechanisms mediated through biliary excretion and subsequent reflux of active metabolites (Wolfe and Soll, 1988).

14.2.2 GI Side Effects Reported in Controlled Clinical Trials

The GI side effects of ASA have been well-characterized and quantified in controlled primary and secondary prevention clinical trials involving tens of thousands of patients. The GI adverse event data from the 5 large primary prevention trials are summarized in the section below demonstrating the consistently low rate of adverse GI side effects from ASA in this population. These adverse GI rates are then shown to be similar to rates reported in meta-analyses of primary prevention, meta-analyses of secondary prevention as well as meta-analyses that integrate the primary and secondary prevention databases.

Because the GI safety risk has been shown to be equivalent across both the primary and secondary prevention databases, and because the mechanism of ASA remains the same no matter the purpose of its use, these data support the conclusion that the risk of GI adverse effects in low and moderate-risk patient populations are both low and predictable based on the entire clinical trial database.

14.2.3 Evidence of GI Side Effects in Randomized Trials for Primary Prevention of Cardiovascular Disease

The 5 primary prevention trials evaluating the use of ASA for the primary prevention of MI serve as the best source of information regarding the GI safety of ASA in individuals at low or moderate-risk of cardiovascular disease events (although it should be noted that ASA intolerant patients were largely excluded from these trials).

14.2.3.1 *Physicians' Health Study (PHS)*

The GI safety endpoints from the PHS are summarized in Table 34 below.

Table 34: Safety Results from PHS: Number of Cases of Significant Adverse Events

Adverse Event	ASA	Placebo	Significance
	No. (%) of patients	No. (%) of patients	
GI symptoms (except ulcer)	3,843 (34.8)	3,779 (34.2)	P=0.48 (n.s.)
Upper GI ulcers	169 (1.5)	138 (1.3)	P=0.08 (n.s.)
Esophageal ulcer	11 (0.1)	6 (0.05)	P=0.23 (n.s.)
Gastric ulcer	25 (0.2)	15 (0.1)	P=0.11 (n.s.)
Duodenal ulcer	46 (0.4)	27 (0.2)	P=0.03
Peptic ulcer	156 (1.4)	129 (1.2)	P=0.11 (n.s.)
Gastrojejunal ulcer	3 (0.03)	4 (0.4)	P=0.70 (n.s.)
Hematemesis*	38 (0.3)	28 (0.3)	P=0.22 (n.s.)
Melaena**	364 (3.3)	246 (2.2)	P<0.00001

Adapted from the Steering Committee of the Physicians' Health Study, 1989

*Vomiting blood; **Rectal bleeding

The authors reported that there was one death in the ASA group from gastrointestinal hemorrhage. The relative risk of ulcer in the ASA group was 1.22 (169 in the ASA group as compared to 138 in the placebo group; 1.5% vs. 1.3%, $p=0.08$). The two groups showed the same incidence of gastrointestinal events aside from ulcer (34.8% in ASA group vs. 34.2% in placebo group, $p=0.48$). The ASA group and the placebo group reported gastrointestinal discomfort equally as frequently (26.1% and 25.6%, respectively; $p=0.45$). 2,979 subjects in the ASA group and 2,248 placebo subjects reported overall bleeding problems, including easy burning, hematemesis, melena, non-specific gastrointestinal bleeding, epistaxis, or other bleeding (relative risk, 1.32; 95% CI=1.25-1.40; $p<0.00001$). Compared to the results in other long-term ASA trials, the frequency and severity of GI discomfort, ulcers, and bleeding attributable to ASA were much lower.

While trends were observed, most GI safety endpoints were not statistically significant. The exceptions were in the rate of duodenal ulcer and melaena.

14.2.3.2 British Doctors' Trial (BDT)

In the BDT, nonfatal peptic ulcer disease was reported significantly more often by subjects taking ASA (46.8 per 10,000 men years vs. 29.6 per 10,000 men years; $2p<0.05$) and there was also a slight excess of nonfatal gastric bleeds reported. However, these excesses did not correspond with an increase in mortality from these causes. The main reason provided for discontinuing ASA treatment was gastrointestinal symptoms. In a

few cases, the symptoms seemed to be alleviated by replacing the 500 mg ASA tablets with 300 mg enteric-coated tablets.

Since side effects can only be attributed to the treatment drug in an unbiased fashion by comparison to placebo, data on side effects from this study add little insight into the true level of risk.

14.2.3.3 Thrombosis Prevention Trial (TPT)

The aim of the Thrombosis Prevention Trial (TPT) was to evaluate low-dose ASA and low-intensity oral anticoagulation with warfarin in the primary prevention of ischemic heart disease (IHD) in a moderate-risk population (The Medical Research Council's General Practice Research Framework, 1998). In this study, 5,499 men at high-risk of IHD aged between 45 and 69 years were recruited from 108 practices in the United Kingdom that belonged to the Medical Research Council's General Practice Research Framework. The participants were deemed to be at a high-risk of ischemic heart disease at entry defined as the top 20% of a risk score distribution based on smoking history, blood pressure, body mass index, blood cholesterol, fibrinogen and factor VII activity. These variables were weighted according to their relationship with ischemic heart disease in the Northwick Park Heart Study (Meade et al., 1986). Individuals were excluded for such reasons as current or recent history of possible peptic ulceration, history of possible or definite MI or stroke, and use of other medication incompatible with trial medication. The four factorial treatment groups were: active ASA and active warfarin (n=1,277), active ASA and placebo warfarin (n=1,268), active warfarin and placebo ASA (n=1,268), and placebo warfarin and placebo ASA (n=1,272). Subjects in this trial were provided 75 mg controlled release ASA daily.

TPT demonstrated a small and insignificant number of major gastrointestinal bleeding episodes. Out of 1,268 subjects in the ASA group, only 5 presented with upper GI bleeding, and there was only one bleeding in an indeterminate location. In comparison, out of 1,272 subjects in the placebo group, there was one event of upper GI bleeding (which was fatal), and one lower GI bleeding event. Two of the major bleeding events, one in the placebo group and one in the ASA group, arose from gastric cancers. There was no significant difference for gastrointestinal bleeding in the ASA group compared to placebo.

14.2.3.4 Hypertension Optimal Treatment (HOT) Study

There were 5 fatal gastrointestinal bleeds in the ASA group and 3 in the placebo group in HOT (see Table 35). Although fatal bleeds (including cerebral) did not differ between the two groups, the overall rate of nonfatal major and minor bleeds (mainly GI and nasal) was about 1.8 times higher in the ASA group. The authors acknowledge that the number of bleeding events for patients in this study is comparable to that reported with the same dose of ASA in secondary prevention trials, where the use of ASA is now considered standard therapy.

Table 35: Safety Results from HOT: Number of Cases of Significant Adverse Events

	ASA (n=9,399)	Placebo (n=9,391)
Fatal GI bleeds	5	3
Nonfatal major GI bleeds	72	34
Minor GI bleeds	30	18

Adapted from Hansson, 1998

14.2.3.5 Primary Prevention Project (PPP)

In PPP, major GI bleedings were more frequent in the ASA group compared to subjects not taking ASA (1.1% vs. 0.3%, $p < 0.0008$). Although existing data documents an increase in GI bleeding, the investigators were reassured by the fact that only one of the bleeding events was fatal. The authors concluded that the safety profile of ASA in the study was acceptable.

Table 36: Safety Results from PPP: Number of Cases of Significant Adverse Events

	ASA (n=2,226)	No ASA (n=2,269)
GI bleeding	17	5
GI disease (except bleeding)	8	3

Adapted from the Collaborative Group of the Primary Prevention Project, 2001

14.2.4 Meta-Analyses of Secondary and Primary Prevention Trials

As stated above, because of the existence of large data sets providing additional information on ASA's GI safety, it is instructive to evaluate whether the GI safety data from these 5 primary prevention studies are confirmed by the vast secondary prevention trial database, particularly since there is no reason to believe that primary prevention patients would be at greater risk for GI bleeding. Meta-analyses that include data from the secondary prevention studies alone, as well as those combining the primary and secondary prevention studies with respect to GI safety are summarized below.

Roderick and colleagues (1993) conducted an overview analysis of 21 placebo-controlled, randomized clinical trials, representing 70,000 person-years of ASA exposure and found that ASA increased the pooled odds ratio (1.5 to 2.0) for gastrointestinal bleeding (including non-major bleeding, e.g., melaena). The risk of upper gastrointestinal symptoms (i.e. nausea, vomiting, heartburn, indigestion) and peptic ulcer

were reported to be 1.7 and 1.3, respectively. While the endpoints are slightly different from the endpoints evaluated in the meta-analyses of the primary prevention studies, the rates appear to be similar and therefore confirmatory.

Dickinson and Prentice (1998) updated the meta-analysis of Roderick and colleagues, including trials of more than one month in duration. They determined that regular ASA use would be associated with about five major gastrointestinal hemorrhages per 1,000 patient-years of exposure, but note that less than half of these events should be attributable to ASA. The investigators conclude that the benefits of ASA therapy outweigh these low risks. It is noteworthy and reassuring that this estimated rate of GI side effects is higher in this analysis of the secondary prevention trials than the rate estimated from analyses of the 5 primary prevention studies (Sudlow, 2001; Hayden et al., 2002).

Weisman and Graham (2002) evaluated the gastrointestinal risks of low-dose ASA (≤ 325 mg/day) when used in FDA-approved secondary prevention of cardiovascular events. Using a computerized literature technique, the investigators reviewed the worldwide published literature to perform a meta-analysis of 6 trials (6,300 patients) using ASA in approved secondary prevention indications. The investigators reported that GI bleeding was a rare finding with only 58 reports across the 6 studies (41 in the ASA groups; 17 in the placebo groups). Only about half of the cases of GI bleeding were deemed severe enough to require treatment withdrawal. There were no reported deaths related to GI bleeding and GI bleeding led to almost no permanent morbidity (i.e., morbidity reported by the investigators of the studies). Only one report, the United Kingdom Transient Ischemic Attack (UK-TIA) trial (Farrell et al., 1991), included in this analysis demonstrated a statistically significant increased risk of GI bleeding as a result of ASA intake. An analysis of GI bleeding across all studies suggests a common risk ratio of 2.5 (95% CI=1.4-4.7; $p=0.001$). Calculation revealed an absolute risk range for GI bleeding of 0% to 2.0% $\pm 1.4\%$ (52-month follow-up). These findings are consistent with the Antithrombotic Trialists' Collaboration comprehensive meta-analysis of randomized trials of antiplatelet therapy published in 2002 (ATC, 2002).

In addition to these meta-analyses evaluating the secondary prevention studies only, the risk of gastrointestinal hemorrhage with long-term ASA use across an array of patient populations (including low, moderate, and high-risk subjects) was assessed in a meta-analysis by Derry and Loke (2000). This analysis evaluated 24 randomized, controlled trials with almost 66,000 participants comparing ASA with placebo or no treatment for a minimum of 1 year (average duration of use was 28 months). Gastrointestinal hemorrhage occurred in 2.47% of patients taking ASA compared with 1.42% taking placebo (odds ratio 1.68; 95% CI=1.51-1.88). At doses below 163 mg/day, gastrointestinal hemorrhage occurred in 2.30% of patients taking ASA compared with 1.45% taking placebo (odds ratio 1.59; CI=1.40-1.81). Meta-regression showed no correlation between gastrointestinal hemorrhage and dose. For modified release formulations of ASA, the odds ratio was 1.93 (CI=1.15-3.23). According to the authors, these data suggest a number needed to harm of 248 per year. These findings are consistent with a series of other meta-analyses that all reported similar relative risks for

GI adverse events from the available clinical trial data (Stalnikowicz-Darvasi, 1995; García-Rodríguez and Jick, 2001; Serebruany et al., 2004; Sibia et al., 2003).

14.2.5 Post-Marketing Experience

Based upon the vast amount of clinical trial data summarized above – including the primary prevention studies, the secondary prevention studies, and meta-analyses combining these data sets – the rate of GI adverse effects appears to be well-established, consistent across studies, and relatively low. 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. Today, over 22 million Americans are 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 reports 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 ≤ 100 mg/day compared with cases mentioning doses > 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 exceeding 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 ≤ 100 mg/day and 4,091 AE reported associated with ASA at doses > 100 mg/day were identified. Of these cases, 66 cases treated with a dose ≤ 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 AE reports, upper GI cases represented 956 cases, 433 for ≤ 100 mg dose, and 523 in 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 (by dividing by 365.25). As shown in Table 37, 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. The rates were reported in terms of patient-years of exposure (py).

Table 37: Worldwide Reporting Rates of Upper GI Cases Based on Patient Exposure as Derived from Sales Data

	ASA ≤ 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 upper GI cases associated with antiplatelet use, 60% (315/525) were associated with ASA doses of ≤ 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 72.5% (313/431) the higher dose.

Table 38: 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 (54.5%)
	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. The median age of the cases with upper GI events is higher than those with other events (Table 39), 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 40).

Table 39: 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 40: 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 upper GI events was higher in those 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 when treated with doses less than or equal to 100 mg/day, 53.1% of upper GI events (230/433) presented with in patients with risk factor(s) vs. 46.9% without in those without a risk factor. Doses greater than 100 mg/day demonstrated that 36.7% of upper GI events (192/523) occurred in patients with risk factor(s) vs. 63.3% in patients without a risk factor (Table 41). When age is also considered a risk factor (> 75 years), the proportion of upper GI events that occurred without any risk factors is reduced from 46.9% (excluding age) to 24.7% in the lower dose groups.

Table 41: 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	37.6%
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 events are associated with the real world use of ASA and that those 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. The following section reviews what is known about the specific factors that influence ASA GI toxicity to guide the development of such an educational effort.

14.2.6 Factors Influencing ASA GI Toxicity

Having concluded that GI adverse events should be expected in a small number of individuals taking low-dose ASA, it is critical to determine what specific characteristics could influence this toxicity. Based upon the totality of the data, the risk of developing GI injury due to ASA may be influenced by a series of factors, including dose, form of ASA (enteric coated or uncoated), duration of use, as well as a series of other potential factors. These potential factors are discussed individually below.

14.2.6.1 Dose

There are a number of studies that have evaluated the dose-response relationship between ASA dose and GI complications. While even low daily doses of ASA such as 100 mg/day (Müller et al., 1989), 75 mg/day (Naschitz et al., 1990; Prichard et al., 1989) or 50 mg/day (Diener et al., 1996) have been shown to be associated with gastroduodenal injury and bleeding, there is no evidence of meaningful differences within the low-dose range (i.e., 75-325 mg/day). However, increased risk of GI effects has been observed in doses in excess of this range.

For example, the UK-TIA Trial (Slattery et al., 1995) demonstrated dose-dependent toxicity and gastrointestinal hemorrhage comparing doses of 300 mg/day and 1200 mg/day to placebo in 2,435 patients. Similarly, a case control study of upper GI bleeding suggested an increased risk of bleeding for ASA doses above 325 mg/day (OR=5.8) compared to doses of \leq 325 mg/day (OR=2.6) (Kelly et al., 1996).

The BRAVO (Blockage of the glycoprotein IIb/IIIa receptor to Avoid Vascular Occlusion) study was a randomized, double-blind, placebo-controlled trial comparing therapy of clopidogrel and ASA to placebo and ASA (Topol et al., 2003). Doses of ASA were not randomly assigned, but rather selected at the discretion of the physician. The investigators found that serious bleeding was more common among patients receiving doses of ASA greater than 162 mg/day (3.3%) compared to those receiving doses of 75-162 mg/day (2.4%), with or without clopidogrel. Based upon the uncontrolled nature of the ASA comparison, it is impossible to make definitive conclusions regarding the impact of ASA dose in this study.

The CURE (Clopidogrel in Unstable angina to prevent Recurrent Event) investigators evaluated the effect of ASA and placebo compared to clopidogrel and ASA on non-specific bleeding events (Peters et al., 2003). There appeared to be a dose-dependent increase in major bleeds from ASA doses less than or equal to 100 mg/day (1.86%) compared to doses greater than 200 mg/day (3.67%) ($p < 0.0001$). Although the authors do not provide the data, they state that the rate of GI bleeding increased significantly with increasing ASA dose in both the placebo and the clopidogrel groups. Importantly, however, because ASA doses were not randomly assigned to subjects, but rather selected at the discretion of the physician, it is impossible to reliably draw the conclusions regarding the effect of dose.

While some have concluded that the 'totality of the evidence' suggests a dose-response relationship for ASA (Cryer, 2002), one of the largest and most comprehensive meta-analyses performed on the available GI toxicity data, (Derry and Loke, 2000) did not detect a statistically significant relationship between ASA dosage and GI bleeding (OR, 1.015 per 100 mg change in dose; 95% CI=0.984-1.047; $p > 0.2$). Cappelleri and colleagues (1995) also failed to find a relationship between GI bleeding and ASA dose from their meta-analysis and meta-regression.

14.2.6.2 Formulation

The form of ASA has been hypothesized to be a variable affecting GI toxicity. Specifically, the enteric-coating is generally considered to be an effective means of protection from gastroduodenal toxicity (Hofteizer et al., 1980; Lanza et al., 1985), and has been associated with a lower degree of endoscopically visible lesions than uncoated ASA (Lanza, 1984; Lanza et al., 1985). Hawthorne and co-workers (1991) compared two different dosages of ASA (300 mg/day and 600 mg/day) with and without enteric coating for 5 days, and found that enteric-coated ASA eliminated the injury caused by the low-dose plain ASA and reduced GI toxicity caused by the high-dose plain ASA. Endoscopic studies also demonstrate better gastric tolerability of enteric-coated ASA preparations (Banoob et al., 2002; Dammann et al., 1999). In a case-controlled study of 1,121 patients, low-dose plain, soluble and enteric-coated ASA tablets for long-term prophylaxis were compared (Weil et al., 1995), and only enteric-coated tablets showed no increased risk of bleeding peptic ulcers. In another study, 300 mg enteric-coated ASA tablets reduced gastric mucosal injury to placebo levels (Cole et al, 1999). There were no gastric erosions in the 300 mg enteric-coated group, whereas gastric erosions were seen in the plain ASA 300 mg group (18 erosions after 5 days) and plain 75 mg

ASA tablets (2 after 5 days); $p=0.003$ compared to plain ASA 300 mg and $p=0.11$ compared to plain ASA 75 mg.

On the other hand, at least two studies demonstrate that there is no decrease in the risk of major upper GI bleeding with the use of enteric-coated or buffered ASA compared to plain ASA. One study determined that buffered ASA is not protective of the gastric mucosa compared to plain ASA, and that the enteric coating does not provide a protective effect (Kelly et al., 1996). Another study demonstrated an increased risk of hospitalization due to upper GI bleeding associated with both plain and enteric-coated ASA at low doses (100 and 150 mg/day), suggesting that the enteric coating does not protect from gastrotoxicity (Sorenson et al., 2000). These groups of investigators have both stated that there is no difference in risk of GI complications with the use of buffered or enteric-coated ASA.

According to the U.S. Prevention Services Task Force (USPSTF, 2002): "Enteric-coated or buffered preparations do not clearly reduce adverse gastrointestinal effects of aspirin." Thus, the data appear to be conflicting as to whether the form of ASA – enteric coated or uncoated – makes a difference in the ultimate likelihood of experiencing adverse GI side effects.

14.2.6.3 Duration of Exposure

Some studies have supported the view that the duration of ASA use influences the risk of developing GI adverse effects (Bombardier et al., 2000; Kurata and Abbey, 1990). In contrast, other studies suggest that the risk of NSAID-induced adverse events, including GI toxicity, is increased immediately in the first 1 to 3 months of use (Gabriel et al., 1991; Lanas et al., 2000; Weil et al., 1995; Slattery et al., 1995). Others have demonstrated that the acute injury occurring shortly after administration of ASA does not have a strong correlation with subsequent clinical effects of mucosal ulceration (Griffin et al., 1991; Langman et al., 1994; Fries et al., 1989; Langman, 1989) or with serious complications (Pounder, 1989; Graham et al., 1988; Larkai et al., 1987). Some have stated that ASA use increases the risk of GI bleeding when used regularly (4 times per week) as well as occasionally, although the risk is higher with regular use (Levy et al., 1988). On the other hand, chronic users have been reported to have a reduced risk of GI complications due to adaptation of gastric mucosa (Sung et al., 2000; Berkowitz et al., 1987; Konturek et al., 1986; Bauer et al., 1986; Baskin et al., 1976; O'Laughlin et al., 1981). Again, as with the effect of ASA form, there appears to be conflicting data as to the effect of duration of ASA exposure on the likelihood of developing GI toxicity.

14.2.6.4 Other Factors

A number of other factors have also been implicated as contributing to the gastrotoxicity of ASA. For example, it is generally agreed that increasing age is a risk factor for GI injury due to ASA use (Fries et al., 1991; Griffin et al., 1991; Henry et al., 1993; Gabriel et al., 1991; Garcia Rodriguez and Jick, 1994; Laporte et al., 1991; Hallas et al., 1995). However, although elderly patients appear to have higher rates of ASA gastrotoxicity

(Silagy et al., 1993), no controlled data establishing a significantly increased risk in elderly populations compared to younger populations are available.

Those that have previously suffered from GI complications from ASA may also be at an increased risk of subsequent GI injury. A history of dyspepsia, uncomplicated peptic ulcers, or bleeding ulcers has been reported to be associated with a higher risk of recurrent ulcer complications with the use of ASA (Fries et al., 1991; Griffin et al., 1991; Garcia Rodriguez and Jick, 1994). On the other hand, there is controversy as to whether or not dyspepsia is a risk factor and some investigators have suggested that the correlation between dyspepsia and ulcers or GI clinical events is weak (Laine, 2001).

Finally, the concomitant use of medications with ASA may increase the risk of adverse GI events. For example, in one cohort study, NSAID plus ASA users had a higher rate of hospitalizations for GI bleeding compared to ASA only users (Sorenson et al., 2000). Concomitant NSAID use increased the chance of bleeding in one controlled study (Weil et al., 1995) and NSAID plus ASA use was shown to double the risk of GI bleeding in other studies (Henry et al., 1993; Sorenson et al., 2000). ASA in combination with anticoagulants such as heparin increased the risk of GI bleeding (Garcia Rodriguez and Jick, 1994). ASA and corticosteroids may also increase the risk of GI toxicity (Nielsen 2001; Gabriel et al., 1991). Laine and colleagues (2004) conducted a double blind, placebo-controlled endoscopic study in 1,615 subjects with osteoarthritis on the rate of ulcer formation with 81 mg enteric coated ASA alone and in combination with rofecoxib, a COX-2 inhibitor. In this study, ASA use alone did not alter the rate of ulcer formation. Dual therapy significantly increased rates of ulcer development compared to ASA therapy alone from baseline to week 12 ($p < 0.001$). These data support the view that concomitant administration of various medications (e.g., NSAIDs, anticoagulants, COX-2 inhibitors) increases the risk of gastrotoxicity. Based on these findings, the U.S. Prevention Services Task Force (USPSTF, 2002) concludes that "...concomitant use of other nonsteroidal anti-inflammatory agents or anticoagulants increase risk for serious bleeding."

14.2.7 Conclusion

In conclusion, based upon a vast amount of consistent and rigorously controlled clinical data, the rate of adverse GI effects from ASA is low and ranges from 0.4 to 1.7 excess major bleeding events per thousand patients treated across the risk spectrum. As would be expected, the rate is similar when estimated from patients at low or moderate baseline cardiovascular risk (i.e., from the primary prevention studies) to that of patients at high baseline cardiovascular risk due to a previous cardiovascular event (i.e., from the secondary prevention studies). 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 is conflicting data 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 growing support for the view that concomitant use of other medications is a significant risk factor for GI toxicity with ASA.

On the other hand, the cardiovascular benefits of ASA therapy are well-documented and support the use of ASA for primary and secondary prevention of cardiovascular disease. These benefits must be weighed against the similarly well-documented, above-stated gastrointestinal risks.

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. Base 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.