

## **B. Statement of Grounds**

### **6. Evaluation of Aspirin Safety**

#### **General Overview**

Aspirin has been used for over 100 years as an analgesic, antipyretic and anti-inflammatory agent and its safety profile is well characterized. However, the discovery that aspirin exerts an inhibitory effect on platelet aggregation has led to its use in cardiovascular disease. Because of the irreversible and cumulative nature of aspirin's anti-platelet effect, low doses of aspirin ( $\leq 325\text{mg}$ ) are effective for prevention of cardiovascular events.

Generally, aspirin toxicity is a dose-related and serious adverse events are extremely rare at lower doses. Contraindications to aspirin use include hypersensitivity to salicylates or other non-steroidal anti-inflammatory drugs (NSAIDs), asthma with rhinitis or nasal polyps, and inherited or acquired bleeding disorders. Aspirin should not be used during pregnancy, particularly in the last trimester due to the risk of complications during and after birth, or in children with chicken pox or flu due to an association with Reye's syndrome. Aspirin should be used with caution in patients with bleeding or platelet disorders, significant dehydration, renal dysfunction (at high doses), erosive gastritis, or peptic ulcer disease. Aspirin should be avoided in severe renal or hepatic failure.

Most of the adverse events reported for aspirin affect the gastrointestinal (GI) system and range from minor complaints such as nausea and dyspepsia, to major events such as ulceration and GI bleeding. The ulcerogenic potential of aspirin and other anti-inflammatory drugs is largely due to inhibition of prostaglandins that protect the gastric mucosa. Since aspirin inhibits platelet aggregation, mucosal injury may be complicated by hemorrhage. Bleeding can also occur at other anatomical sites. Minor events such as bruising and epistaxis can occur with aspirin use, and more serious events such as hemorrhagic stroke are seen in rare instances.

Similarly, allergic reactions observed with the use of aspirin are usually minor (rashes, itching, urticaria). More serious anaphylactic or dermal reactions are very rare. A cross-sensitivity between aspirin and other NSAIDs has been demonstrated. Central nervous system effects seen with aspirin are rare and generally minor (eg. dizziness, insomnia). Tinnitus and reversible hearing loss have been seen at high aspirin doses at the

upper limit of the therapeutic range. Although reversible hepatic transaminase elevations have been reported with chronic, high dose aspirin therapy, and NSAIDs have been reported to cause renal adverse effects via prostaglandin inhibition in the renal vasculature, the use of aspirin is precluded only in severe hepatic or renal failure.

Interactions with aspirin have been reported with methotrexate, valproic acid, older sulfonylurea agents, other anti-platelet agents or anticoagulants, and certain antihypertensives and diuretics. These effects are dose dependent.

The safety profile of aspirin has been developed mainly from experience with analgesic and anti-inflammatory use. Several factors distinguish the use of aspirin in cardiovascular prevention from its use for analgesic and anti-inflammatory indications. Dosing is typically lower than that used for analgesia and inflammation, but the duration of use is long-term rather than episodic. Patients at risk for cardiovascular events are more likely to have underlying disease (eg., diabetes mellitus, hypertension, hyperlipidemia) and more likely to be using other medications. For these reasons, it is most relevant to review the adverse events reported in the large, controlled trials specific for the primary prevention indication.

## Safety in Primary Prevention Trials

### Overview

The five major primary prevention trials: Physicians' Health Study <sup>1,2</sup>(PHS), British Male Doctors' Trial <sup>3</sup> (BMD), Thrombosis Prevention Trial <sup>6</sup>(TPT), Hypertension Optimal Treatment Trial <sup>7</sup>(HOT), and Primary Prevention Project Trial <sup>9</sup>(PPP) have been summarized herein. Data for these studies are summarized in Table 10.

**Table 10. Five Primary Prevention Trials**

	<b>PHS</b>	<b>BMD</b>	<b>TPT*</b>	<b>HOT</b>	<b>PPP</b>
Subjects	Healthy males	Healthy males	High CVD risk males	Males and females with DBP 100-115 mm Hg	Males and females with $\geq 1$ risk factor
Age	40-84 years	<80 years	45-69 years	50-80	$\geq 50$ years
Treatment (N)	325mg qod (11,037)	300-500mg qd (3429)	75mg qd (1268)	75mg qd (9399)	100mg qd (2226)
Control (N)	Placebo (11,034)	No aspirin (1710)	Placebo (1272)	Placebo (9391)	Vit E 300mg (2231)
Duration	3.8-6.4 yr Mean 5 yr	5-6 yr	Median 6.8 yr	3.3-4.9 yr Mean 3.8 yr	Mean 3.6 yr

\*warfarin treatment groups were not considered relevant for this comparison.

Subjects included in these trials had no prior cardiovascular event, but had varying degrees of cardiovascular risk. In the PHS and BMD trials, only healthy subjects were enrolled. In the HOT and PPP trial, at least one major cardiovascular disease (CVD) risk factor was required. In the TPT, subjects had comparatively high CVD risk scores as calculated from major CVD risk factors.

These studies were large, and while powered to detect differences in numbers of cardiovascular events and other efficacy endpoints, after more than 55,000 subjects were treated for an average of at least 3.8 years, adverse events were relatively rare. Therefore, the numbers of serious gastrointestinal and hemorrhagic serious adverse events were small; many comparisons of adverse event rates for aspirin with control groups were not statistically significant; and in general, confidence intervals were wide.

Most subjects enrolled in these trials were white males. Some subgroup analyses were performed to assess differences in the effects of aspirin therapy with age, gender and in persons with concurrent disease (eg hypertension and diabetes), but numbers were small. In studies with male and female subjects, gender differences in adverse event rates were not observed, and none would be expected based upon what is known about the safety of aspirin when used for other indications.

As expected, minor gastrointestinal complaints and minor bleeding episodes were reported in all of the primary prevention trials. In these trials, the most important adverse events that had an impact on morbidity and mortality associated with aspirin therapy were hemorrhagic stroke and serious gastrointestinal events. Therefore, these events will be the focus of this discussion.

### *Trial Synopses*

- *Physicians' Health Study*

In this study, 1.53% of subjects using aspirin experienced an upper gastrointestinal ulcer as compared to 1.25% in the placebo group (RR 1.22,  $p=0.08$ ). Among those with ulcer, ~22% in the aspirin group experienced hemorrhage compared to ~16% in the placebo group (RR 1.77,  $p=0.04$ ). One death from gastrointestinal hemorrhage was reported in the aspirin group. In the aspirin group, hemorrhagic strokes were seen in 0.21% of subjects compared to 0.11% in the placebo group ( $p=0.06$ ). Minor bleeding events (bruising, hematemesis, melena, epistaxis) occurred significantly more frequently in the aspirin group (RR 1.32,  $p<0.00001$ ). The difference in the percent of subjects experiencing minor gastrointestinal discomfort in the treatment group versus placebo was not significant.

- *British Doctor's Trial*

Nonfatal peptic ulcer was reported significantly more often in subjects in the aspirin group than the control group (2.6% vs 1.6% respectively,  $p<0.05$ ), but a difference in death due to GI perforation or hemorrhage was not observed. In this study, the majority of strokes observed were not differentiated by subtype (ischemic vs hemorrhagic). Of those cases where subtype was determined, the rate of occurrence of hemorrhagic stroke did not differ significantly between active and control groups (0.38% vs 0.35% respectively).

- *Thrombosis Prevention Trial*

Major gastrointestinal bleeding episodes occurred in 0.47% of all patients in the aspirin group and 0.16% of patients in the placebo group, but the difference was not statistically significant. Intermediate gastrointestinal bleeds were observed in 1.26% of patients taking aspirin vs 0.63% in the placebo group, but this difference was also not statistically significant. Hemorrhagic (including sub-arachnoid) strokes were seen in 0.24% of patients in the aspirin group and 0.16% of subjects in the placebo group (difference not significant). It was noted however, that the mean systolic blood pressure was significantly higher in men who experienced a hemorrhagic stroke than in men who experienced another type of stroke, or in men who did not experience a stroke. The percent of patients experiencing any minor bleeding event at any site in the aspirin group was significantly higher than the placebo group (38.2% vs 31.3%,  $p < 0.001$ ).

- *Hypertension Optimal Treatment Trial*

Significantly more patients (1.37%) in the aspirin group experienced non-fatal major bleeding (all sites) compared to those in the placebo group (0.75%) (risk ratio 1.8,  $p < 0.001$ ). Fatal or non-fatal gastrointestinal bleeding was experienced by 0.85% of aspirin patients, and 0.39% of placebo patients (statistical significance not reported). Fatal or non-fatal cerebral bleeding was experienced by 0.15% of aspirin patients, and 0.16% of placebo patients (statistical significance not reported). Minor bleeding episodes was reported almost twice as frequently in the aspirin group.

- *Primary Prevention Project Trial*

Severe non-fatal bleeding complications (all sites) were experienced more in the aspirin group compared to the control group (1.1% patients vs 0.3% patients,  $p = 0.0008$ ). This finding was largely driven by gastrointestinal bleeding. Similarly, severe non-fatal gastrointestinal bleeding or disease was experienced by 0.8% of the aspirin patients and 0.2% of the control patients (significance not reported). There was no significant difference in the percent of patients experiencing hemorrhagic stroke between the aspirin (0.09%) and control groups (0.13%).

### Hemorrhagic Stroke and Intracranial Bleeding

Hemorrhagic stroke data from all trials are summarized in Table 11, adapted <sup>21</sup>

**Table 11: Hemorrhagic Stroke / Intracranial Hemorrhage in Primary Prevention Trials**

	% patients with event		Odds ratio (95%CI)	Events caused (or avoided) per 1000 patients treated with aspirin per yr
	aspirin	Control		
PHS	0.21	0.11	1.92 (0.95 – 3.86)	0.20
BMD	0.38	0.35	1.08 (0.41 - 2.85)	0.05
TPT	0.24	0.16	1.51 (0.25 – 9.03)	0.12
HOT	0.15	0.16	0.93 (0.45 – 1.93)	(0.03)
PPP	0.09	0.13	0.67 (NR)	(0.12)

The effect of blood pressure on the occurrence of hemorrhagic stroke was investigated in several trials. In the PHS, there was no consistent effect, but in the TPT there was an association with systolic blood pressure elevation. Not surprisingly in the HOT trial, where blood pressure was controlled, there was no difference in the occurrence of hemorrhagic stroke between the treatment and control groups. The effect of age as an independent risk factor for hemorrhagic stroke has not been conclusively demonstrated in these primary prevention trials or in the meta-analysis by He et al. <sup>22</sup>

In all studies, the difference in the percent of patients experiencing a hemorrhagic stroke or intracranial bleed (aspirin vs. placebo) did not reach statistical significance, due to the very rare occurrence of these events (Table 11). A meta-analysis using data from these trials also failed to demonstrate statistical significance, and estimated an odds ratio of 1.4 (CI, 0.9 - 2.0) corresponding to an excess risk with aspirin of 0.1 event per 1000 patients-years <sup>21</sup>.

The USPSTF recently evaluated data on hemorrhagic stroke and approximated the risk associated with the use of aspirin therapy in primary prevention is 0.2 events per 1000 patient-years. That is, for every 1000 patients treated for a 5-year period, aspirin therapy would be expected to cause 1 hemorrhagic stroke.

### Major Gastrointestinal Events

Major gastrointestinal event data from all trials is summarized in Table 12, adapted <sup>21</sup>. Types of events captured and reported for each trial are different, but are the best estimates available for estimating overall gastrointestinal safety.

**Table 12. Major Gastrointestinal Events in Primary Prevention Trials**

	Type of Event	% subjects with event (number of fatalities)		Significance	Events caused per 1000 patients treated with aspirin per yr
		aspirin	Control		
PHS	Upper GI ulcer	1.5 (1)	1.3 (0)	p=0.08	0.4
BMD	Peptic ulcer	2.6 (3)	1.6 (3)	P<0.05	1.7
TPT	Serious GI bleeding	1.7 (0)	0.8 (1)	NS	1.3
HOT	Major GI bleeding	0.8 (5)	0.4 (3)	Not reported	1.1
PPP	Severe GI bleeding	0.8 (0)	0.2 (0)	Not reported	1.5

In each of these trials, patients on aspirin therapy experienced a greater number of serious gastrointestinal events than did controls. A meta-analysis of these trials focused on major extracranial bleeding, and an odds ratio for aspirin therapy was estimated to be 1.7 (CI 1.4 to 2.1), or an excess risk for major (mostly gastrointestinal) bleeding events of 0.7 (CI, 0.4 to 0.9) per 1000 patient-years <sup>21</sup>. This estimate is similar to the findings of a meta-analysis of secondary prevention trials <sup>23</sup>, where pooled odds ratios of 1.5 to 2.0 for gastrointestinal bleeding for aspirin therapy were estimated. Additionally, a meta-analysis of 24 trials with >1 year of aspirin therapy <sup>24</sup> found that aspirin use increased the risk of gastrointestinal hemorrhage to a similar extent (Odds Ratio 1.68, CI 1.5-1.9).

Therefore, it is reasonable to estimate that for every 1000 patients treated for a 5-year period, aspirin primary prevention therapy would be expected to cause an average of 3 significant gastrointestinal bleeding episodes.

### **Overall Risk**

These estimates of risk are useful in helping the physician use risk / benefit tools. The physician needs to consider other factors that influence risk and the suitability of aspirin therapy for every patient. In addition, these risks must be clearly communicated to the patient, who should take part in the decision making process. Most importantly, patients should be made aware of symptoms that may indicate an adverse event. Early recognition can facilitate management and prevent a more serious outcome.