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The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials

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The proven benefit of aspirin in the secondary prevention of cardiovascular disease and its possible value in primary prevention must be weighed against its potential hazards. This paper is an overview of the gastrointestinal toxicity of aspirin, its most serious complication after intracerebral haemorrhage. Information on toxicity has been drawn only from randomised trials, thus avoiding the potential biases of observational studies. All randomised placebo controlled trials listed in the Anti-platelet Trialists Collaboration where a direct aspirin-placebo comparison was possible were included. Twenty-one trials were included, all but one of secondary prevention. There were over 75,000 person years of aspirin exposure. The pooled odds ratios for categories of gastrointestinal bleeding (e.g. haematemesis, melaena) were between 1.5–2.0; fatal bleeds were very rare. The risk of peptic ulcers was 1.3 and of upper gastrointestinal symptoms 1.7. These risks were lower than those found in observational studies. Attributable disease rates are also presented. For haematemesis for example they varied from 0.2–1.0 per 1000 person years. Toxicity was dose related. Aspirin does have significant gastrointestinal toxicity, although this is rarely fatal. More recent work has demonstrated the efficacy of low doses of aspirin (75 mg daily) but there is limited information yet available on its toxicity.

Keywords aspirin toxicity gastrointestinal bleeding

Introduction

The value of aspirin in the secondary prevention of cardiovascular disease is well established. The Anti-platelet Trialists Collaboration (APTC) showed that aspirin reduced the odds of fatal vascular events by 15% and of non-fatal events by 30% (Antiplatelet Trialists Collaboration, 1988). However, the role of aspirin in primary prevention is less clear. The US physicians trial found a significant 44% reduction in non-fatal myocardial infarction in men randomised to aspirin (325 mg on alternate days) but no difference in vascular deaths was demonstrable (Steering Committee of the Physicians' Health Study Group, 1989). There was a 20% increase in strokes in men given aspirin, though it was not statistically significant. The British doctors trial found no reduction in myocardial infarction, but also suggested a possible excess of strokes (Peto *et al.*, 1988).

Much of the increasing use of aspirin in both primary and secondary prevention will occur outside the close follow-up of clinical trial settings, particularly as aspirin is available without prescription. This highlights the importance of establishing the hazards of aspirin as well as its efficacy. The main side-effect of aspirin is bleeding, the most serious manifestation being intra-cerebral haemorrhage, followed by gastrointestinal bleeding. For stroke, the value of aspirin depends on the balance between any reduction in thrombotic events, which account for about three-quarters of major strokes, and a possible increase in haemorrhagic episodes. However, it is still the exception rather than the rule for strokes to be investigated by imaging at the appropriate time so that thrombotic and haemorrhagic events can be differentiated.

This paper reviews the evidence for aspirin-related gastrointestinal bleeding and other upper gastrointestinal toxicity derived from randomised controlled trials. Most of these trials have used daily doses of aspirin of 300 mg or more. The gastrotoxicity of aspirin at lower doses, is also of interest. Preliminary findings from the Thrombosis Prevention Trial, a randomised double-blind placebo controlled trial of low dose aspirin, 75 mg daily, and low dose warfarin in the primary prevention of coronary heart disease in men at high risk (Miller, 1989) are considered. We also discuss the results of some recently published trials which have used low doses of aspirin.

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Methods

All vascular disease prevention trials which were included in the Anti-Platelet Trialists Collaboration (1990) where aspirin was used were considered. Criteria for inclusion in this paper were:

1. Randomised double-blind placebo controlled trial.
2. Follow-up for 1 year or more.
3. Gastrointestinal toxicity reported in a form allowing events and symptoms to be defined in a reasonably standard manner.
4. Direct aspirin *vs* placebo comparison possible.

The list of these trials is shown in Table 1. All reported gastrointestinal toxicity was reviewed. There was considerable variation in the definition of symptoms, signs and clinical diagnoses, and in the comprehensiveness with which they were reported. For example, a diagnosis of 'haematemesis' could have been reported within the categories 'ulcer and haematemesis', 'haematemesis leading to withdrawal', 'gastrointestinal bleeding', 'admission with g.i. bleeding', or 'g.i. bleeding leading to withdrawal'. Consequently, different trials were included in the analyses of these different categories. Some gastrointestinal events can manifest in several ways at the same time, and hence it is inappropriate to make inferences about overall risk by combining categories. Only when side effects were reported in the same way in more than one trial were the results of those trials pooled.

The odds ratio for aspirin use *vs* placebo for each side-effect in each trial was calculated by the method described by Yusuf *et al.* (1985). This is a measure of the relative risk of an event occurring in patients taking aspirin compared with those taking placebo. 99% confidence limits are given for odds ratios in individual trials and 95% confidence limits for the pooled result. The area of the square around each point estimate in the Figures is proportional to the amount of information contributed (i.e. to the variance of the observed minus expected).

For each side-effect, between-trial heterogeneity was tested by the chi-squared test. Only for epigastric pain was there some evidence of heterogeneity (χ^2 6.9 $P = < 0.03$), one of 11 tests performed. This symptom, reported in three trials, is therefore not included in this analysis. Rates attributable to aspirin were calculated for all trials with over 500 patients randomised to aspirin, using the method described by Rothman (1986). This is a measure of the absolute event rate specifically due to aspirin.

Results

Trials included

There were 21 trials with a total of 20,011 subjects being randomised to aspirin and 19,635 to placebo (Table 1). The average follow-up for all trials combined was 3.85 years giving a total 76,215 person years of exposure to aspirin (excluding trial 24 which did not give the average follow-up). The majority of subjects (over 80%) were male. The mean age was not calculable but most patients were middle-aged.

Table 1 Randomised controlled trials of aspirin *vs* placebo

Trial	*Number entered* ASA	Placebo	*Age (years)*	*Sex*	*Condition*	*Daily dose (mg)*	*Mean follow-up (years)*
Steering Committee of the Physicians' Health Study Research Group (1989)	11037	11034	—	M	Primary	160	5.16
Fields *et al.* (1977)	88	90	Md 60	MF	TIA	1300	2
Bousser *et al.* (1983)	198	204	Mn 63	MF	TIA/CVA	990	3
The Canadian Cooperative Study Group (1978)	144	139	—	MF	TIA	1300	2.16
Sorensen *et al.* (1983)	101	102	Mn 59	MF	Rev CVA	990	2.1
Britton *et al.* (1987)	253	252	Mn 68	MF	CVA	1500	2
Boysen *et al.* (1988)	150	151	Mn 59	MF	Post CE	50–100	1.75
UK-TIA (1988)	806/815	814	Mn 60	MF	TIA/minor CVA	300/1200	4
Petersen *et al.* (1989)	336	336	Md 74	MF	Chronic AF	75	2
Elwood *et al.* (1974)	615	624	Mn 55	M	Post MI	300	1
Elwood & Sweetnam (1979)	832	850	Md 57	MF	Post MI	900	1
The Persantin-Aspirin Reinfarction Study (1980)	810	406	Md 59	MF	Post MI	975	3.4
The Aspirin Myocardial Infarction Study (1980)	2267	2257	Mn 63	MF	Post MI	1000	>3
The Coronary Drug Project Research Group (1976)	727	744	—	M	Post MI	972	1.84
Breddin *et al.* (1980)	317	309	R45–70	MF	Post MI	1500	2
Cairns *et al.* (1985)	139	139	Mn 57	MF	Unstable angina	1300	1.5
McEnany *et al.* (1982)	71	77	Md 51	MF	CABG	1200	1.8
Hess *et al.* (1985)	67	69	Mn 62	MF	PVD	990	2
DAMAD Study Group (1989)	157	157	Mn 47	MF	DM	990	3
Ehresmann *et al.* (1977)	215	213	Mn 59	MF	PVD	1500	?
Vogel *et al.* (1979)	672	668	—	MF	Post MI	1500	1.75

Md, median; CE, carotid endarterectomy; R, range; MI, myocardial infarction; TIA, transient ischaemic attack; CABG, coronary artery bypass graft; Mn, mean; PVD, peripheral vascular disease; DM, diabetes mellitus; CVA, cardiovascular accident; AF, atrial fibrillation.

The daily dosages (number of trials) used in the trials were 50–100 mg (n = 2), 100–499 mg (n 3), 500–999 mg (n = 7) and 1 g or more (n = 10). In one trial (UK TIA) two doses of aspirin, i.e. 300 and 1200 mg, were used.

The trials were based on patients with myocardial infarction (n = 7), TIA or stroke (n = 6), atrial fibillation (n = 1), unstable angina (n = 1), peripheral vascular disease (n = 2), diabetic retinopathy (n = 1), and patients who had undergone arterial grafting (n = 2). The US physicians trial was of primary prevention.

Patients excluded from the trials

In 81% of trials (17/21), a history of peptic ulcer and/or gastrointestinal bleeding, or contraindication to aspirin was definitely stated as an exclusion criterion. In four, exclusion criteria were not stated (UK-TIA Study Group, 1988; Elwood *et al.*, 1974; Hess *et al.*, 1985; Ehresmann *et al.*, 1977).

Gastrointestinal bleeding

Table 2 and Figure 1 present individual and pooled results for the six main symptoms or diagnostic categories of gastrointestinal bleeding which were specified in the same way in more than one trial. Although several of the trials have small numbers of events resulting in wide confidence intervals, the overview shows a consistent and significant increase due to aspirin in all categories, with the pooled odds ratios ranging between 1.5 and 2.0. However, not all of this bleeding is from the upper gastrointestinal tract. The 'all g.i. bleeding' category

Table 2 Odds ratios for gastrointestinal bleeding

Trial	*Number in aspirin group*	*Observed events*	*Obs-Exp*	*Odds (99% CI) ratio*
Haematemesis				
Steering Committee US Physicians (1989)	11037	38	5.0	1.4 (0.7–2.6)
AMIS (1980)	2267	14	3.5	1.9 (0.6–6.0)
The Coronary Drug Project (1976)	727	3	0.5	1.5 (0.2–15.4)
		Pooled		1.5 (1.0–2.2)
Melaena				
Steering Committee US Physicians (1989)	11037	364	59.0	1.5 (1.2–1.8)
AMIS (1980)	2267	61	11.4	1.6 (1.0–2.7)
The Coronary Drug Project (1976)	727	20	4.7	1.9 (0.7–4.7)
		Pooled		1.5 (1.3–1.8)***
Bloody stools				
AMIS (1980)	2267	111	22.8	1.7 (1.2–2.6)
The Coronary Drug Project (1976)	727	22	0.8	1.1 (0.5–2.4)
		Pooled		1.6 (1.2–2.1)**
All gastrointestinal bleeding				
UK TIA[1] (1988)	815	38	12.5	2.8 (1.3–5.7)
UK TIA[2] (1988)	806	21	4.1	1.6 (0.7–4.0)
Petersen *et al.* (1989)	336	1	0.5	7.4 (0.0–1276.7)
Elwood & Sweetnam (1979)	832	8	2.1	2.0 (0.5–8.9)
The Persantin-Aspirin Reinfarction Study (1980)	810	33	5.7	1.9 (0.8–4.5)
McEnany *et al.* (1982)	71	0	0	— —
Hess *et al.* ((1985)	67	4	1.5	3.5 (0.3–35.8)
Fields *et al.* (1977)	88	1	0.5	7.6 (0.0–1306.4)
The Canadian Cooperative Study Group (1978)	144	0	−1.0	0.1 (0.0–5.0)
Britton *et al.* (1987)	253	3	0.5	1.5 (0.2–15.1)
Ehresmann *et al.* (1977)	215	1	−0.5	0.5 (0.0–10.0)
		Pooled		2.0 (1.5–2.8)***
Gastrointestinal bleeding leading to trial withdrawal				
Elwood & Sweetnam (1979)	832	8	2.1	2.0 (0.5–8.9)
The Persantin-Aspirin Reinfarction Study (1980)	810	28	4.7	1.9 (0.7–4.7)
Breddin *et al.* (1980)	317	3	1.5	7.3 (0.4–142.7)
DAMAD (1989)	157	0	−0.5	0.1 (0.0–23.4)
Bousser *et al.* (1983)	198	1	0.5	7.6 (0.0–1316.7)
Elwood *et al.* (1974)	615	0	0	
		Pooled		2.0 (1.1–3.6)*
Hospital admissions for gastrointestinal bleeding				
UK TIA[1] (1988)	815	19	6.0	2.6 (0.9–7.1)
UK TIA[2] (1988)	806	12	2.6	1.7 (0.5–5.7)
The Persantin-Aspirin Reinfarction Study (1980)	810	12	0.7	1.2 (0.3–4.6)
		Pooled		1.9 (1.1–3.1)*

[1]UK TIA 1200 mg daily.
[2]UK TIA 300 mg daily.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$.

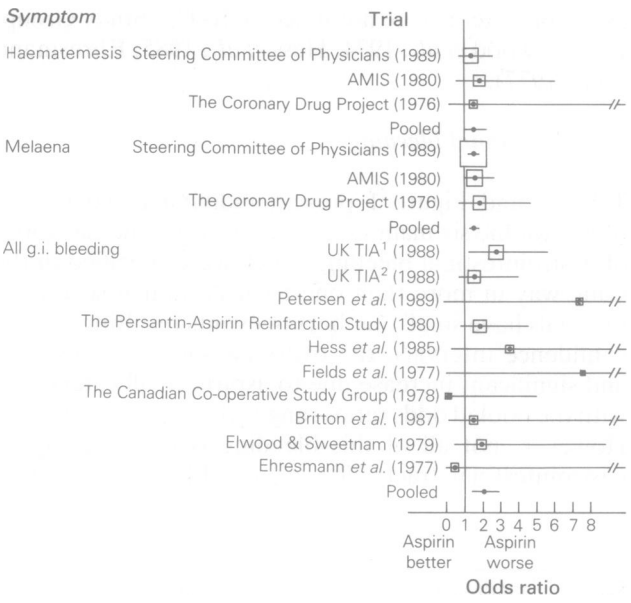

Figure 1 Odds ratios for gastrointestinal bleeding (1 = 1200 mg dose, 2 = 300 mg dose).

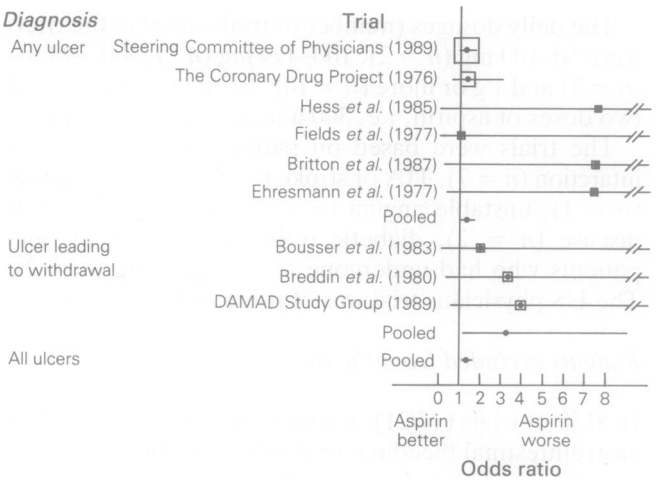

Figure 2 Odds ratios for peptic ulceration.

includes any g.i. site and rectal bleeding is likely to be predominant.

In the UK TIA trial there were two fatal events on aspirin on the 1200 mg dose, none on 300 mg and two on placebo (UK-TIA Study Group, 1988).

There was a significantly increased need for blood transfusion in the US physicians trial and in the AMIS trial, with odds ratios of 1.7 (0.9–3.1) and 2.4 (1.0–6.0) respectively (AMIS, 1980; Steering Committee of the Physicians' Health Study Research Group, 1989).

Peptic ulcer

The pooled odds ratio of developing a peptic ulcer on aspirin compared with placebo was 1.3 (1.0–1.6) (Table 3, Figure 2), with the US physicians trial providing the majority of the person-years of exposure (Steering Committee of the Physicians' Health Study Research Group, 1989). Duodenal and gastric ulcers were not distinguished, except in a proportion of cases in the US physicians trial (Steering Committee of the Physicians' Health Study Research Group, 1989).

Upper gastrointestinal symptoms

The risk of developing any upper gastrointestinal symptoms (i.e. nausea, vomiting, heartburn, indigestion) was 1.7 (1.5–1.8), with a similar result for symptoms severe enough to lead to trial withdrawal (Table 4, Figure 3). Three trials (AMIS, 1980; The Persantin-Aspirin Reinfarction Study, 1980; The Coronary Drug Project Research Group, 1976) reported the odds ratios for the individual symptoms vomiting and heartburn, which when pooled were 2.9 (1.8–4.6) and 2.2 (1.9–2.7) respectively. In the US physicians trial the proportions reporting gastrointestinal discomfort were virtually the same in the aspirin and placebo groups, 26% and 25.6% respectively.

Table 3 Odds ratios for peptic ulcer

Trial	*Number in aspirin group*	*Observed events*	*Obs-Exp*	*Odds (99% CI) ratio*
Any ulcer				
Steering Committee US Physicians (1989)	11037	169	15.5	1.2 (0.9–1.7)
The Coronary Drug Project (1976)	727	20	2.2	1.3 (0.5–3.1)
Hess *et al.* (1985)	67	1	0.5	7.6 (0.0–1316.1)
Fields *et al.* (1977)	88	1	0.0	1.0 (0.0–39.5)
Britton *et al.* (1987)	253	2	1.0	7.4 (0.2–283.3)
Ehresmann *et al.* (1977)	215	3	1.5	7.4 (0.4–145.7)
		Pooled		1.3 (1.0–1.6)*
Ulcer leading to withdrawal from trial				
Bousser *et al.* (1983)	198	2	0.5	2.0 (0.1–38.6)
Breddin *et al.* (1980)	317	4	1.5	3.3 (0.3–32.9)
DAMAD (1989)	157	5	2.0	3.9 (0.5–32.3)
Elwood *et al.* (1974)	615	0	0	— —
		Pooled		3.2 (1.1–9.0)*
All ulcers (1 + 2 combined, 10 trials)				1.3 (1.07–1.6)
Hospital admission				
AMIS (1980)	2267	29	12.0	4.1 (1.7–10.0)

*$P < 0.05$.

Table 4 Odds ratios for upper gastrointestinal symptoms

Trial	*Number in aspirin group*	*Observed events*	*Obs-Exp*	*Odds (99% CI) ratio*
All upper g.i. symptoms (nausea, vomiting, pain)				
Sorensen *et al.* (1983)	101	9	1.0	1.3 (0.4–5.1)
UK TIA[1] (1988)	815	316	58.8	2.0 (1.5–2.6)
UK TIA[2] (1988)	806	237	20.6	1.3 (1.0–1.7)
Hess *et al.* (1985)	67	20	4.2	2.0 (0.7–5.6)
Cairns *et al.* (1985)	139	64	9.5	1.8 (0.9–3.3)
The Persantin-Aspirin Reinfarction Study (1980)	810	147	13.1	1.4 (0.9–2.2)
AMIS (1980)	2267	537	99.5	1.8 (1.5–2.1)
		Pooled		1.7 (1.5–1.8)***
Upper g.i. symptoms leading to withdrawal				
Bousser *et al.* (1983)	198	6	2.1	2.9 (0.5–17.9)
Boysen *et al.* (1988)	150	3	−0.5	0.8 (0.1–5.4)
Breddin *et al.* (1980)	317	16	2.3	1.4 (0.5–4.0)
McEnany *et al.* (1982)	71	3	0.1	1.1 (0.1–9.3)
DAMAD (1989)	157	6	2.0	2.8 (0.4–17.6)
Peterson *et al.* (1989)	336	4	0.5	1.3 (0.2–9.4)
Elwood *et al.* (1974)	615	0	0	— —
The Persantin-Aspirin Reinfarction Study (1980)	810	147	13.0	1.4 (0.9–2.2)
		Pooled		1.5 (1.1–1.9)**

[1]UK TIA 1200 mg daily.
[2]UK TIA 300 mg daily.
$^{**}P < 0.01$; $^{***}P < 0.0001$.

Withdrawal from trial due to side-effects

This was reported in 15 trials but is non-specific as it includes withdrawal for any reason thought to be due to active treatment. The pooled odds ratio was 1.4 (1.2–1.6).

Effect of aspirin dose

The UK TIA trial (1988) allows a direct comparison of 300 mg and 1200 mg daily doses. The odds ratio for g.i. bleeding was 2.8 (1.3–5.7) for the 1200 mg daily dose and 1.6 (0.7–4.0) for 300 mg. The smaller dose was also associated with a lower risk for 'all upper g.i. symptoms' and 'for hospital admissions due to a g.i. bleed'. Figure 4 shows the odds ratios of trials using 300 mg or less *vs* those using over 300 mg. There is no significant difference between the three clinical categories but there is a consistent tendency for a smaller risk in the lower dose trials.

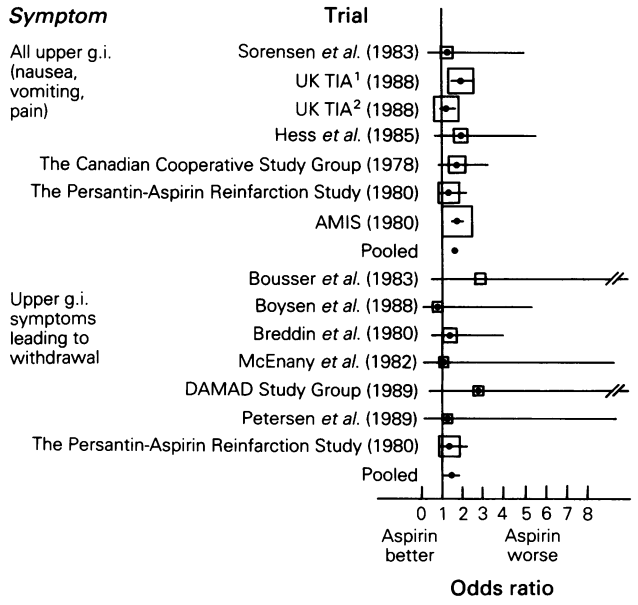

Figure 3 Odds ratios for upper gastrointestinal symptoms (1 = 1200 mg dose, 23 = 300 mg dose).

Rates attributable to aspirin

Table 5 shows the rate of occurrence of the main symptoms attributable to aspirin for trials with over 500 patients randomised to aspirin. For example, in the US physicians trial there was a 40% increase in the risk of haematemesis, and this resulted in about 1 additional event per 5000 person years.

Thrombosis prevention trial

This primary prevention trial in high risk men uses 75 mg aspirin daily and low intensity oral anticoagulation (International Normalised Ratio 1.5) in a placebo-controlled factorial design. Over 1000 person years of

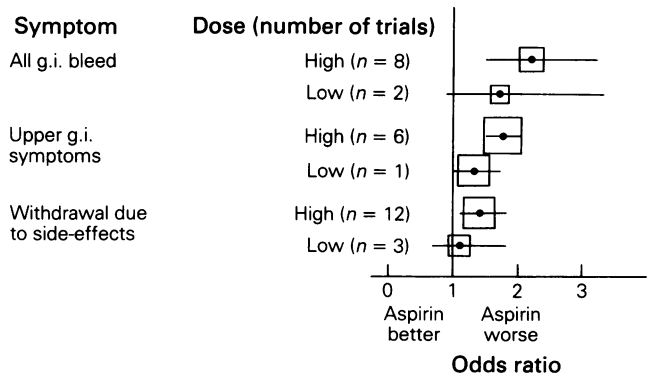

Figure 4 Effect of aspirin dose (high = > 300 mg dose, low = ≤ 300 mg daily).

Table 5 Rates attributable to aspirin

Symptom	*Trial*	*Percentage* increase in rate*	*Attributable rate (events/1000 person years)*
Haematemesis	Steering Committee of the Physicians' Health Study Research Group (1989)	40	0.2
	AMIS (1980)	90	1.0
	The Coronary Drug Project (1976)	50	0.8
Melaena	Steering Committee of the Physicians' Health Study Research Group (1989)	50	2.1
	AMIS (1980)	60	3.4
	The Coronary Drug Project (1976)	90	7.0
All g.i. bleed	UK TIA (1988) (1200 mg)	180	7.7
	UK TIA (1988) (300 mg)	60	2.5
	The Persantin-Aspirin Reinfarction Study (1980)	90	6.2
Peptic ulcer	Steering Committee of the Physicians' Health Study Research Group (1989)	20	0.5
	The Coronary Drug Project (1976)	30	3.3
Hospital admission for peptic ulcer	AMIS (1980)	310	3.5

*Point estimates derived from odds ratios.

Table 6 Thrombosis prevention trial

	Upper gastrointestinal toxicity	
	Active aspirin placebo warfarin	*Double placebo*
Number of men	907	932
Person-years	1045	1057
Upper g.i. bleeding[1]	2	0
Non-bleeding upper[2] g.i. pathology	1	4
Indigestion[3] *n* (%)	245(27)	245(26)
Nausea or vomiting[3] *n* (%)	82(9)	84(9)

[1]One 'duodenitis', one 'oesophagitis and duodenitis'.
[2]Diagnosed by barium meal or endoscopy or operatively.
[3]Self-reported at clinic visits.

exposure have accrued in each of the four treatment groups. Table 6, confined to those on active aspirin alone or on double placebo (i.e. omitting those on active warfarin, either with placebo or active aspirin) shows that there have been two major upper gastrointestinal bleeds (neither fatal) in the active aspirin (placebo warfarin) group and none in the double placebo group. There is no excess of non-bleeding gastric pathology or of associated symptoms.

Discussion

For most types of toxicity considered, pooled odds ratios ranged between 1.5 and 3.0. These may be underestimates of the true risk because compliance, as judged by tablet counts, platelet aggregation tests and urinary salicylate was not complete. For example, tablet counts suggested that the proportion of tablets taken ranged from 63% to 98%. Moreover, between 5–15% of subjects taking placebo had positive platelet aggregation or urine tests.

The pooled odds ratio for haematemesis was 1.5. This figure is heavily weighted by the US physicians study, which used a relatively low dose (equivalent of 160 mg daily) and in which the odds ratio was 1.4. In the AMIS trial (1980), which used 1.4 g daily, the odds ratio was higher at 1.9. However, neither of these results were significantly different from 1.0. These estimates of risk are lower than those derived from case-control studies. In a review of case-control studies by Hawkey there was an odds ratio of 3.3 for upper g.i. bleeding and in a recent case-control study it was even higher at 7.2 (Hawkey, 1990; Laporte *et al.*, 1991). The RCT largely avoids the difficulties faced by observational studies, such as selection and recall biases and confounding.

In the US physicians trial, the attributable risk of haematemesis due to aspirin was approximately 0.2 events per 1000 man years, and in AMIS it was 1.0, which may be partly explained by the differences in doses used (160 mg *vs* 1 g daily equivalent). The risks of 'melaena' and 'all g.i. bleeding' were higher than for 'haematemesis' but such diagnoses are not specific for bleeding from the upper g.i. tract since they may include, for example, bleeding piles. Fatal g.i. bleeding was rarely reported. In the UK TIA trial, there were two deaths in the 1200 mg arm but none in the 300 mg arm in over 3000 person years in each arm.

The relative risk of any peptic ulcer was 1.3. This estimate is again dominated by the finding of the US physicians trial. Nevertheless in the Coronary Drug Project trial, the odds ratio was also 1.3 despite the higher aspirin dose of 1.4 g. Although the UK doctors trial was not included in the overview because it was not

placebo controlled, the estimate of the relative risk of peptic ulceration was similar, at 1.6 (Peto *et al.*, 1988). However, the odds ratio for hospital admission for peptic ulcer in the AMIS trial was 7.7 (Kurata & Abbey, 1990). The site of the ulcer was not specified except in the US physicians study, but even here most were classified as peptic. It is not possible, therefore, to confirm or refute the finding from Hawkey's review of case-control studies that aspirin consumption is associated mainly with gastric ulcers, his pooled odds ratio being 4.7 for gastric ulcers but only 1.2 for duodenal ulcer. In the later analysis of the AMIS trial, aspirin increased the risk of hospitalisation in men for both gastric and duodenal ulcers (Kurata & Abbey, 1990). The point estimates of the attributable risk of peptic ulcer due to aspirin, derived from the US physicians and CDP trials, were 0.5 and 3.3 events per 1000 person years respectively, although the confidence limits will be wide.

Symptoms of upper gastrotoxicity were consistently raised in subjects taking aspirin and contributed to a greater withdrawal rate due to side-effects.

Case-control studies have not been able to evaluate the effect of the dose of aspirin used. In the UK TIA trial, the odds ratios for 'all g.i. bleeding' and 'upper g.i symptoms' among those taking 1200 and 300 mg were 2.8 and 1.6 and 2 and 1.3 respectively. The limited analysis in this review which includes other trials and 'withdrawals due to side effects' also suggests that higher doses have greater toxicity. In terms of efficacy, the APTC showed no difference between 300 mg and higher doses, and in the US physicians trial a daily equivalent of 160 mg produced a significant reduction in non-fatal MI. There is consequently great interest in even lower dose preparations (under 100 mg). In the RISC trial, 75 mg daily lead to a two-thirds reduction in recurrent MI or death in patients with unstable angina over three months follow-up (The RISC Group, 1990). Two studies have used low doses in the secondary prevention of stroke in patients with previous TIA or minor stroke. The SALT trial found that 75 mg daily led to a significant 18% reduction in stroke or death from any cause compared with placebo, and the Dutch TIA group found that 30 mg daily may be as efficacious as 283 mg in preventing secondary vascular events (SALT Collaborative Group, 1991; The Dutch TIA Trial Study Group, 1991). Doses as low as 40 mg daily have led to gastric mucosal bleeding when given to healthy volunteers for short periods (Prichard *et al.*, 1987). In the SALT trial (1991) there was a non-significant excess of g.i. bleeding, odds ratio 2.6 (0.7–9.9), and g.i. symptoms, odds ratio 1.2 (0.8–1.9). In the Thrombosis Prevention Trial, two events of upper gastrointestinal bleeding have so far occurred in the aspirin only arm and none in the placebo arm, with a daily dose of 75 mg (Meade *et al.*, 1993). The Dutch TIA group (1991) found that the 30 mg dose produced a third fewer major g.i. bleeds than the 283 mg dose.

The most likely sources of bias or imprecision in this review are the heterogeneous nature of the reporting of side effects, differences in aspirin dose and in the underlying risks of subject populations. Where the effects were not reported, it is not clear whether none occurred, whether there was no difference or whether the information was not obtained. For these reasons the pooled estimates may need to be interpreted with caution. Nevertheless, it can be concluded that the regular use of aspirin in daily doses up to 1.5 g increases the risk of upper g.i. bleeding, peptic ulceration and g.i. symptoms (which may in turn reduce compliance). It is possible that the relative and absolute risks of aspirin derived from RCTs are somewhat conservative estimates of the actual risks in day to day usage. Even so fatalities are rare and the side-effects are probably fewer at lower doses. These risks must be set against the convincing evidence of therapeutic efficacy in the secondary prevention of cardiovascular disease. Further evidence of efficacy in primary prevention and of the toxicity of low doses is needed.

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