Review

Aspirin: benefit and risk in thromboprophylaxis

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Summary

Aspirin is often perceived either as a harmless panacea or as a useless poison which causes endless, needless trouble. We have carefully reviewed the literature on all aspects of aspirin and find that neither view is justified. Regular use of even low-dose aspirin (150 mg/day or less) may lead to clinically-important adverse events, particularly haemorrhage. The risk of such an event is considerably outweighed by the benefit for patients with a significant risk of a thromboembolic event. For individuals without a clear risk of thrombosis or thromboembolism, the balance is more even: indiscriminate aspirin-taking is to be discouraged.

Introduction

One hundred years after its commercial launch as ‘Bayer Aspirin’, acetyl salicylic acid (2-acetoxybenzoic acid) must be the most widely used medication in the world. Since our experience is that half or more of the elderly population of the UK is now taking regular, low-dose aspirin, either prescribed by a doctor or self-prescribed, we have reviewed the balance of clinical benefit and risk of aspirin use. We have reviewed particularly data from blinded randomized efficacy trials, but refer to other sources. Our specific objective has been to assess the bleeding associated with aspirin use and to balance this with the benefits in prevention of vascular disease.

Over a century before Hoffmann developed a process for bulk preparation of stable acetyl salicylic acid (the compound had been first documented in 1853), the Reverend Edward Stone wrote from Chipping Norton on April 25th, 1763, to the then President of the Royal Society the following: ‘There is the bark of an English tree, which I have found by experience to be a powerful astringent, and very efficacious in curing anguish and intermitting disorders.’ The active principle in infusions of willow bark was later characterized as saligenin (the glucoside of salicyl alcohol) which is doubly a pro-drug of salicylic acid. Hoffmann’s search for a pro-drug presentation of salicylic acid which would be reliably absorbed and tolerable in the large doses required for analgesia unwittingly gave us a new drug, aspirin, with clinical actions and a specific pharmacological activity which are quite separate from the activities of the salicylic acid to which it is readily converted in the body.

Clinical pharmacology of aspirin

Aspirin is readily hydrolysed to yield salicylic acid, in the gut to a small extent, during transit through the gut wall, more rapidly during first-pass metabolism in the liver, as a concomitant of acetylation of plasma and other proteins, and by plasma hydrolases. There is some evidence that, particularly at lower dosages, the platelet inhibitory effect is inversely correlated with hydrolysis rate in plasma. At all doses, systemic exposure to salicylate is considerably greater than for aspirin itself, since the half-life of aspirin in blood is less than 20 min, while that of salicylate is rather more than 2 h.

Aspirin ingestion leads rapidly to inhibition of...
platelet aggregation and prolongation of skin bleeding time. Several days are required for these haemostatic functions to return to pre-ingestion levels, as the platelet, having no nucleus, cannot replace inhibited enzymes and recovery is dependent on the rate of new platelet formation: the bleeding time recovers more quickly. The substantial literature on the influence of dose, timing and formulation on aspirin’s pharmacodynamic effects has not been systematically reviewed recently, but several papers give a feel for the complexities. An adequate dose, generally >100 mg single dose rapidly absorbed, or >40 mg daily, will result in a rapid and sustained inhibition of both collagen-induced aggregation and the second wave of ADP-induced aggregation of platelets ex vivo, and extension of skin bleeding time by a maximum factor of about 2.5. In ‘poor responders’ 5–10-fold greater doses may be required to see an effect, and there are some individuals who seem not to respond even at higher doses. Hawkey et al. have shown that in healthy subjects bleeding from the gastric mucosa in response to a standard insult (biopsy) is increased by aspirin ingestion, with no difference between 300 mg od and 600 mg qds dosing, while McGurk and Dinsdale have shown that the frequency of vacuum-induced petechiae on oral mucosa is not increased at 12 h after a single 325 mg dose. In both studies, skin bleeding times were significantly increased.

These pharmacodynamic actions, which are much greater than those induced by salicylate or other non-steroidal anti-inflammatory agents (NSAIDs), derive from aspirin’s unique chemical action as an affinity label, transferring its acetyl group to the Ser residue of the constitutive cyclo-oxgenase (prostaglandin H synthase) type 1 enzyme (COX–1), leading to complete and irreversible inactivation of the enzyme. The equivalent residue on the isozyme, COX–2 (which is constitutive at low activities in most cells including platelets but which is inducible to high activities in inflammatory cells and some somatic cells during the inflammatory reaction) is much less efficiently acetylated. However, high concentrations of salicylic acid reversibly inhibit COX–2, explaining its anti-inflammatory, analgesic and febrifuge activities. Accumulated high concentrations of salicylate can also block aspirin access to the Ser site of COX–1, but the practical importance of this is not clear. PGH₂ is metabolized in platelets entirely to thromboxane A₂ (Tx-A₂), a powerful platelet aggregator which mediates collagen-induced aggregation, the platelet release reaction and the second phase of ADP-induced aggregation. In vascular endothelial cells, PGH₂ is metabolized largely to prostacyclin (PGI₂) a powerful inhibitor of platelet aggregation which also can cause disaggregation of early platelet aggregates. PGH₂ is also the precursor in gastric mucosa for the cytoprotective and vasodilatory PGE₂ in inflammatory cells of PGE₁ which sensitizes nociceptors to pain signals, and for a host of other mediators and effectors (see e.g. Hawkey and Rampton).

Platelets and polymorphonuclear cells also possess 12-lipoxygenase (12-LO) activity. The stable product of 12-LO action, 12-hydroxyeicosatetraenoic acid (12-HETE), is implicated in platelet adhesion and spreading on subendothelial matrix and vascular endothelial cells. It is thus a key substance in the formation both of haemostatic plugs and arterial thrombi and, a fortiori, in the skin bleeding test. 12-HETE production by platelets or whole blood in response to collagen is inhibited by aspirin, but appears to recover within a few hours. Platelet 12-LO activity appears to be susceptible to inhibition by aspirin in some individuals and not in others, and it has been suggested that in those individuals in whom it is not inhibited but COX–1 is, excess arachidonic acid may be shunted down the pathway to 12-HETE giving rise to enhanced haemostatic or thrombotic tendencies. There is some evidence that patients who have a good bleeding time extension in response to aspirin have better therapeutic responses: this distinction has been built into the BRAT study, the results of which are awaited. On the other hand, Gimple and colleagues have found strong evidence that extended bleeding time is strongly correlated with increased spontaneous bleeding after fibrinolysis following myocardial infarction. It may be that the antithrombotic and pro-haemorrhagic effects of aspirin run strictly in parallel.

**Side-effect profile**

The daily dose of aspirin required required for thromboprophylaxis is much lower than that needed for effective relief of pain or inflammation. Salicylates, and particularly aspirin, are still widely used in high doses (>2 g/day) as analgesics, and have long been known to cause a variety of side-effects, particularly tinnitus, the classic symptom of salicylism, and (in common with most other NSAIDs), a range of symptoms and metabolic derangements which may be severe enough to be lethal (detailed in Martindale, pp. 17 et seq. and 72). All these unwanted effects are the result of excessive chronic use or overdosing. For the pharmacokinetic reasons given above, the side-effect profile of aspirin necessarily includes that of salicylic acid, although at the dosages now commonly employed for thromboprophylaxis (<300 mg/day) this does not present clinical problems.

The mechanisms associated with aspirin toxicity
are, in contrast to its antithrombotic action, still controversial. Aspirin, in common with salicylate and most other NSAIDs, has been associated with gastric mucosal irritation and erosions with microscopic blood loss, progressing to ulceration and frank, even catastrophic, bleeding into the gut at any level, causing haematemesis or melaena (summarized by Scott\textsuperscript{28}): gastrointestinal bleeding is frequently reported in aspirin overdose. The possibility of exacerbated bleeding as an extension of aspirin’s beneficial pharmacodynamic effect on haemostasis is much greater than is the case with other NSAIDs.\textsuperscript{29}

There are several clinical situations (Table 1) in which aspirin might cause or exacerbate bleeding. The practical question is to what extent aspirin is responsible for precipitating or increasing the severity of events in these situations. The answer is by no means complete, but we shall examine three types of data, namely from randomized clinical trials, from case-control and similar studies, and from direct experimental examination.

Haemorrhage is the most clinically important side-effect of aspirin use. Individual clinicians vary widely in their perception of how frequently this occurs. Commonly, individuals who have a history of dyspepsia or peptic ulceration are not prescribed long-term aspirin to reduce vascular occlusion, either in routine practice or in clinical trials. The proportion of patients who may be intolerant due to dyspepsia is uncertain, anecdotally between 5 and 25%. However, even in the remainder there is the small chance that some severe bleeding, such as intracranial haemorrhage or major gastrointestinal haemorrhage, might cause early disability or death. In each clinical context, such events must be balanced against the benefit of aspirin in preventing or deferring life-threatening infarction, stroke or pulmonary embolism.

### Randomized clinical trial data

**Aspirin and gastrointestinal bleeding**

The efficacy data and most of the safety data from randomized, controlled, trials involving antiplatelet agents has been well summarized by the Antiplatelet Trialists’ Collaboration.\textsuperscript{30–34} Roderick, Wilkes and Meade\textsuperscript{34} restricted their analysis of adverse events to long-term trials with adequate reporting. They showed that aspirin use significantly increases the risk of severe gastrointestinal upset or bleeding by odds ratios ranging from 1.5 to 2.0, the increase being independent of narrow sub-category of event. Similar odds ratios were obtained for minor gastric symptoms, whether leading to cessation of treatment or not. Death as a result of gastrointestinal bleeding was very rare. Peptic ulcers were reported 30% more frequently by aspirin takers (odds ratio about 1.3) but this estimate was very heavily influenced by data from one study. Roderick and colleagues showed further that, for each type of gastrointestinal event considered—all bleeds, all symptoms and treatment cessations due to symptoms—the odds ratios for dosing with 300 mg/day or less were consistently lower than for dosing with >300 mg/day, though never significantly different. The limited data on doses currently favoured for thromboprophylaxis (40–150 mg/day) could not show whether gastrointestinal toxicity might be even less with these lower

### Table 1 Assessing the risks of aspirin use

**Practical questions to be answered:**

1. ‘What are the adverse events associated with aspirin use?’
2. ‘For those adverse events which may also occur in the absence of aspirin taking, does aspirin increase:
   - the incidence of such events?’
   - the average severity of such events?’
   - the absolute number of such events requiring intervention?’

**Specific circumstances for which answers are required:**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Peri-surgical bleeding</th>
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<tr>
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<td>Post-surgical bleeding</td>
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<td></td>
<td>Re-operation/transfusion requirements</td>
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<td></td>
<td>Thrombolysis and anticoagulation</td>
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<td></td>
<td>Ruptured intra-cranial aneurysm</td>
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<td>Ruptured peptic ulcer/haematemesis/melaena</td>
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<td></td>
<td>Parturition</td>
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<td></td>
<td>Haemorrhagic stroke</td>
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<td></td>
<td>Persistent GI or renal blood loss</td>
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<td></td>
<td>Epistaxis</td>
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<td></td>
<td>Haemoptysis</td>
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<tr>
<td></td>
<td>Easy bruising; petechiae; gingival bleeding</td>
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</tbody>
</table>

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Surgery Peri-surgical bleeding
Post-surgical bleeding
Re-operation/transfusion requirements
Thrombolysis and anticoagulation
Ruptured intra-cranial aneurysm
Ruptured peptic ulcer/haematemesis/melaena
Parturition
Haemorrhagic stroke
Persistent GI or renal blood loss
Epistaxis
Haemoptysis
Easy bruising; petechiae; gingival bleeding
doses. However, the investigators in two important studies of low-dose regimens published since Roderick et al.’s review, the Dutch TIA Study and SALT, have concluded independently that ‘75mg still causes a significant excess of bleeding events compared to placebo’, and ‘nor are low-dose aspirin regimens [30 mg/day] of any advantage in reducing haemorrhagic strokes’ as compared with medium/high ones.

Examination of the more recent studies (Tables 2 to 5) confirms that adverse events are rarely defined and recorded with the objectivity accorded to outcome events, although a recent study found the distinction between major and minor bleeding episodes to be reproducible and clinically relevant. The WHO nomenclature of side-effects is rarely used, so exact comparisons between trials are difficult, and even the methods of ascertainment are not consistent between trials. In general, questionnaires and frequent direct questioning of in-patients in short-term studies will produce more frequent records of more trivial events, while pragmatic reliance on the patient actively complaining may miss minor events. Clearly, the potential toxicity of aspirin in the general population is greater than that reported in clinical trials, since candidate trial subjects with gastrointestinal symptoms have usually been excluded: however, this exclusion mirrors clinical practice where patients complaining of such symptoms will not be prescribed aspirin.

Data published since the second round APTC overview (Table 3) broadly confirm and extend the

Table 2  Summary of benefits* of aspirin treatment found in trials since the Second Round APTC Overview

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of probable reduction in rates of early and late graft occlusion in coronary artery by-pass surgery: range of 4 to 46 absolute reduction per 1000 patients treated (compared with mean 92 in APTC 1994 Part II)—5 studies. Practical advantages but probably no efficacy advantage over anticoagulation—2 studies.</td>
<td>1</td>
</tr>
<tr>
<td>No reduction in brain or eye emboli in heart valve replacement patients, but positive effect on all cause mortality—2 studies.</td>
<td>1</td>
</tr>
<tr>
<td>Satisfactory analgesia after minor surgery—1 study. In immediate post-stroke period, reduces all cause mortality by 4 to 5, death or dependency by about 12, and stroke recurrences by 5 to 11, per 1000 patients treated—2 major studies.</td>
<td>1</td>
</tr>
<tr>
<td>Started in middle stages of pregnancy, may reduce significantly incidence of pre-eclampsia (9–17/1000 women treated), intra-uterine growth retardation and premature delivery (25 ± 9/1000 women treated) in at-risk pregnancies—2 studies.</td>
<td>1</td>
</tr>
</tbody>
</table>

*In addition to previously-identified effects on vascular events.

earlier assessments of the gastrointestinal toxicity of aspirin, although the estimate of relative risk for major bleeding is rather higher. Combining the earlier overview with the newer data (Table 5), we conclude that patients treated with aspirin for extended periods will suffer about five major and 14 minor gastrointestinal bleeding events and about 70 other gastrointestinal symptoms per 1000 patient-years of exposure: less than half of these events are directly attributable to aspirin use. These disadvantages are outweighed by the benefits (Table 6), confirming that all patients at high risk of vascular thrombotic events should be given aspirin unless there is a strong contraindication. It must be remembered also that the vascular events averted by aspirin are, in terms of quality-adjusted life years, far more serious than the vast majority of the haemorrhagic effects attributable to aspirin.

Aspirin and surgical bleeding

Part III of the second round APTC overview gives some information on peri- and post-operative bleeding complications. The need for transfusion of peri-operative bleeds was 7/1000 patients in the antiplatelet treated groups (mostly aspirin) and 4/1000 patients in the control groups, based on up to 4000 patients in each group. The data in Table 7 suggest an increase of peri-operative blood loss of about 30% (or about half a standard deviation) in patients taking aspirin in the 7 days before surgery. This may be controlled by aprotinin or vasopressin treatment, by inhibition of fibrinolysis or increasing Factor VIII levels. Surgeons are concerned about intra-operative as well as post-operative bleeding, but most studies have not distinguished the two types of haemorrhage sufficiently for comment to be made. However, Kallis et al. noted that surgeons do no better than chance in deciding whether a patient has taken aspirin pre-operatively, assessed on operation site oozing.

Anaesthetists have been concerned by the possibility of subdural bleeding in patients undergoing regional anaesthesia, especially with pre-operative anticoagulant or antiplatelet use. In a retrospective series of 1013 episodes of anaesthesia in 805 patients undergoing orthopaedic surgery, Horlocker, Wedel and Ofiord found that no patient had a subarachnoid or epidural haematoma or any post-operative neurological deficit: however, there was an increase of about threefold to 3.5% in the incidence of blood in the needle aspirate in those patients taking aspirin (on average about 2 g/day). In contrast, the CLASP investigators and Sibai and the NICHD Network collaborators found no excess of even minor bleeding complications of epidural anaesthesia in women taking 60 mg/day aspirin. Surgeons have a further worry that they may have to carry out surgical
### Table 3  Summary of data on gastrointestinal symptoms

| Study source | Aspirin dose (mg/day) | Major bleeds | | Minor bleeds | | Any other GI effect |
|--------------|----------------------|--------------|----------------|----------------|-------------------|
|              | Absolute rate*       | Relative risk** | Absolute rate* | Relative risk** | Absolute rate* | Relative risk** |
| van der Meer et al., 1993; 1994 | 10 | 10 | | | | |
| Diener et al., 1996 | 25 | <42§ | 1.85§ | | 156† | 1.10 |
| CLASP, 1994 | 60 | <1.0 | | <1.0 | | |
| Sibai et al., 1993 | 60 | <2.5 | | <2.5 | | |
| Meade et al., 1992 | 75 | 8.5 | 1.7 | 42 | 1.15 | |
| Goodman et al., 1994 | 80 | <53 | | | | |
| Theilman et al., 1994 | 100 | | | | | |
| Turpie et al., 1993 | 100 | 17 | 2.0 | | | |
| Sanz et al., 1990 | 150 | <10 | | 194 | 3.0 | |
| Silagy et al., 1993 | 200 | 30 | | | | |
| Yli-Mäyry et al., 1992 | 250 | 6*** | | | | |
| McCollum et al., 1991 | 300 | 11 | | 0.65 | | |
| UK-TIA Study 117 | 300 | 7 | | 2.5 | | |
| Gavaghan et al., 1991 | 324 | <8 | | 47 | 1.9 | |
| CAPRIE, 1996 | 325 | 5 | | | | |
| Chesebro et al. 1983 | 500 | 39 | | | | |
| VA Cooperative Group, 1988 | 975 | <4 | | | | |
| UK-TIA (1988 & 1995) | 1200 | 11 | | 4.0 | | |
| EPSIM, 1982 | 1500 | 12 | | | | |
| 17 studies; 26,057 subjects treated: 39,409 patient-years exposure | | | | | | |
| Range | 10–1500 | | | | | |
| Simple medians: | | | | | | |
| | | | | | | |
| Weighted medians: | | | | | | |
| | | | | | | |
| Roderick, Wilkes & Meade, 1993 | 75–1500 | | | | | |
| 21 studies; 20,817 subjects treated: 75,000 patient-years exposure | | | | | | |

* Events/1000 patient-years. ** Compared to management without aspirin. *** Identified bleeding ulcers. § Assigning all recorded bleeds as gastro-intestinal. † Half of these events were epigastric pain.
Table 4  Summary of data on non-gastrointestinal bleeding events

<table>
<thead>
<tr>
<th>Study source</th>
<th>Aspirin dose (mg/day)</th>
<th>Intra-cranial bleeds</th>
<th>Other major bleeds</th>
<th>Any other effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute rate*</td>
<td>Relative risk**</td>
<td>Absolute rate*</td>
<td>Relative risk**</td>
</tr>
<tr>
<td>Diener et al., 1996†</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van der Meer et al., 1994†</td>
<td>50</td>
<td>1.5</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Meade et al., 1992‡</td>
<td>75</td>
<td></td>
<td>27</td>
<td>1.0</td>
</tr>
<tr>
<td>Goodman et al., 1994§</td>
<td>80</td>
<td></td>
<td>(7/114pt)</td>
<td></td>
</tr>
<tr>
<td>Turpie et al., 1993#</td>
<td>100</td>
<td>15.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>CAST, 1997##</td>
<td>160</td>
<td>16§</td>
<td>1.24</td>
<td>8§</td>
</tr>
<tr>
<td>Silagy et al., 1993###</td>
<td>200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IST, 1997###</td>
<td>325</td>
<td>9§</td>
<td>1.08</td>
<td>11§</td>
</tr>
<tr>
<td>CAPRIE, 1996###</td>
<td>325</td>
<td>0.26</td>
<td>&lt;38</td>
<td></td>
</tr>
<tr>
<td>Chesebro et al., 1983##</td>
<td>500</td>
<td>1.3</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Théroux et al., 1988###</td>
<td>650</td>
<td>0</td>
<td>0</td>
<td>(3/245pt)</td>
</tr>
<tr>
<td>EPSIM, 1982###</td>
<td>1500</td>
<td>0.6</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

- All bleeding events 42 1.87
- Epistaxis 105 1.45
- Haematuria 25 1.27
- Bruising 125 1.64
- Microscopic haematuria 23/114pt 1.09
- 1.67
- Other minor bleeds 1.09
- Haematuria 1.09
- Other minor bleeds 1.09
- All bleeding events 20 2.11
- Haematuria 0.6
Table 5 Conclusions from randomized, prospective studies

<table>
<thead>
<tr>
<th>Simple median</th>
<th>Weighted median</th>
</tr>
</thead>
<tbody>
<tr>
<td>X: 4.6</td>
<td>X: 2.0</td>
</tr>
</tbody>
</table>

Fewer than 1 in 10 patients undergoing major surgery while on aspirin have any operation site complication (bleeding/infection).

Fewer than 1 in 100 patients taking aspirin long-term suffer any kind of bleeding event in a year.

Aspirin, in short courses or long-term, increases the incidence and severity of bleeding complications by a factor of between 1 and 2 times.

Less than half of the events occurring in aspirin takers are attributable to aspirin.

It is generally not possible to determine whether a haemorrhage has been specifically caused by aspirin.

The evidence for a dose-event rate relationship is weak: that is, attributable events occur even at the lowest doses adequately investigated (60–75 mg/day).

Peri- and post-operative bleeding may be controlled by vasopressin or aprotinin infusion. Transfusion requirements may be minimised by re-infusion of drain fluids.

Patients taking regular moderate (>1 g/day) doses of aspirin may have an asymptomatic mild anaemia.

Aspirin is often given post-partum or after dental surgery for pain control, but bleeding complications have not been recorded in large comparative trials. Reports which appear to have been influential in persuading some dentists to require cessation of aspirin before extractions are both old and, being based on rather small numbers, anecdotal; however, in these studies, pre-operative aspirin which caused moderate increase of the bleeding time did not cause any appreciable increase in peri-operative blood loss.
Table 6  Estimated mean overall benefits of aspirin treatment from APTC 1994 Part 1

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>Reduction of events/1000 patients</th>
<th>Vascular death</th>
<th>Non-fatal myocardial infarction</th>
<th>Non-fatal strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>in 1 month treatment</td>
<td>24</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Prior MI</td>
<td>per year</td>
<td>5.5</td>
<td>8</td>
<td>2.6</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>per year</td>
<td>4</td>
<td>3.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Other high risk</td>
<td>per year</td>
<td>5</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Low risk (primary prevention)</td>
<td>per year</td>
<td>0.1</td>
<td>1</td>
<td>−0.4</td>
</tr>
<tr>
<td>All surgical</td>
<td>in 2–8 weeks treatment</td>
<td>Fatal + non-fatal pulmonary emboli—17</td>
<td></td>
<td></td>
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</tbody>
</table>

Intracranial bleeding

Intracranial bleeds (haemorrhagic strokes and ruptured aneurysms) are clinically the most important complications. A wide range of absolute rates of intracranial haemorrhage in aspirin-treated groups is evident in the small studies from the second round APTC overview and trials published subsequently (Table 4). Other than in the immediate post-ischaemic-stroke period, the rates seem to be small, around 1 per 1000 patient years of exposure: less than half of these events are attributable to aspirin. In the immediate post-ischaemic-stroke period the rate will also include haemorrhagic conversion of the original ischaemic stroke. The rate is about 10/1000 patients treated during 2–4 weeks (seeming to be rather more than 10 times higher than in long-term use), but only between 7 and 20% of these events may be attributable to aspirin.

Case control and other studies

In addition to randomized trials involving aspirin, many, mainly small, observational studies have been published from which it is difficult to calculate haemorrhagic rates, although they generally accord with the randomized studies. Amongst such studies, Taggart, Siddiqui and Wheatley note that summary figures are always distorted by outliers (heavy bleeder), even in the no-treatment group: this is a good reason for using medians (as has been done in Tables 3 and 4, above) and interquartile or 90% ranges to summarize data with a wide distribution, rather than the seemingly ubiquitous mean (SD). The experience of different surgical teams varies widely, and few investigators set out rigid criteria for re-operation in the study protocol. It is interesting that Reich et al. reported no re-operations for bleeding in 197 consecutive patients undergoing coronary artery bypass grafting (CABG), approximately half of whom were taking aspirin, giving an estimated maximum rate in the aspirin group well below any listed in Tables 7 and 8.

In a case-control study of re-operation rates in CABG patients, Bashein et al. report that patients taking aspirin within 7 days prior to surgery have a re-operation rate 1.82 (1.23–3.32) times higher than non-aspirin-takers. The authors comment that this complication entails longer intensive care and general hospital residence as well as increased use of blood products, and that aspirin in the pre-operative period should be avoided, if possible. Bischof et al. concluded from a long-term retrospective follow-up study on a 292 patients that, while life-long aspirin use might slightly prolong median survival time in carotid endarterectomy patients, it did not cause any detectable increase in intracranial haemorrhage. Otley et al. concluded from a retrospective series and a review of the literature that the excess of haemorrhagic complications following minor cutaneous surgery in patients taking aspirin was minimal.

The case-control study information shows some sort of consensus on risks for the gastrointestinal complications of aspirin use. The incidence of clinical and other studies

In addition to randomized trials involving aspirin, many, mainly small, observational studies have been published from which it is difficult to calculate haemorrhagic rates, although they generally accord with the randomized studies. Amongst such studies, Taggart, Siddiqui and Wheatley note that summary figures are always distorted by outliers (heavy bleeder), even in the no-treatment group: this is a good reason for using medians (as has been done in Tables 3 and 4, above) and interquartile or 90% ranges to summarize data with a wide distribution, rather than the seemingly ubiquitous mean (SD). The experience of different surgical teams varies widely, and few investigators set out rigid criteria for re-operation in the study protocol. It is interesting that Reich et al. reported no re-operations for bleeding in 197 consecutive patients undergoing coronary artery bypass grafting (CABG), approximately half of whom were taking aspirin, giving an estimated maximum rate in the aspirin group well below any listed in Tables 7 and 8.

In a case-control study of re-operation rates in CABG patients, Bashein et al. report that patients taking aspirin within 7 days prior to surgery have a re-operation rate 1.82 (1.23–3.32) times higher than non-aspirin-takers. The authors comment that this complication entails longer intensive care and general hospital residence as well as increased use of blood products, and that aspirin in the pre-operative period should be avoided, if possible. Bischof et al. concluded from a long-term retrospective follow-up study on a 292 patients that, while life-long aspirin use might slightly prolong median survival time in carotid endarterectomy patients, it did not cause any detectable increase in intracranial haemorrhage. Otley et al. concluded from a retrospective series and a review of the literature that the excess of haemorrhagic complications following minor cutaneous surgery in patients taking aspirin was minimal.

The case-control study information shows some sort of consensus on risks for the gastrointestinal complications of aspirin use. The incidence of gastrointestinal bleeding severe enough to bring the patient to hospital appears enhanced by a factor between 1 and 10 times, perhaps depending on the formulation of aspirin, the dose taken and the prior duration of use. In one informative study, two series of controls were collected, one from the general community and the other from hospital in-patients (excluding those admitted with acute MI). It was clear that aspirin use correlated with hospitalization for all reasons other than MI, yet the only causal relation inferred from this data was for gastrointestinal bleeding. But Weil et al. found that 75% of ulcer bleeds admitted were not associated with aspirin use. In brief, patients who are ill enough to be hospitalized take aspirin more frequently than healthy controls. If a section of the population has a medical condition that predisposes both to the adverse event and to taking the drug, drug-takers would be over-represented in
Table 7  Summary of peri-traumatic event data

<table>
<thead>
<tr>
<th>Study</th>
<th>Nature of trauma</th>
<th>Aspirin dose (mg/day)</th>
<th>Peri-traumatic bleeds—‘major’ or requiring reoperation</th>
<th>Peri-traumatic blood loss</th>
<th>Per-operative transfusion requirement**</th>
<th>Other events</th>
<th>Absolute rate</th>
<th>RRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Meer et al., 1994¹¹⁰</td>
<td>Coronary artery bypass</td>
<td>50</td>
<td>46</td>
<td>—</td>
<td>—</td>
<td>1.07</td>
<td>671</td>
<td>1.00</td>
</tr>
<tr>
<td>Sanz et al., 1990¹¹⁴</td>
<td>Graft operation</td>
<td>150</td>
<td>35</td>
<td>0.81</td>
<td>1256</td>
<td>1.07</td>
<td>671</td>
<td>1.00</td>
</tr>
<tr>
<td>Yli-Mäyry et al., 1992¹¹⁵</td>
<td></td>
<td>250</td>
<td>30</td>
<td>—</td>
<td>1296 ± 760</td>
<td>—</td>
<td>5390 ± 2062</td>
<td>—</td>
</tr>
<tr>
<td>Gavaghan et al., 1991⁹⁶</td>
<td></td>
<td>324</td>
<td>47</td>
<td>5.2</td>
<td>902</td>
<td>0.97</td>
<td>732</td>
<td>1.03</td>
</tr>
<tr>
<td>Chesebro, 1990¹²³</td>
<td></td>
<td>975</td>
<td>51</td>
<td>3.9</td>
<td>1087</td>
<td>1.40</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>VA Co Group, 1988²⁰</td>
<td></td>
<td>975</td>
<td>51</td>
<td>3.9</td>
<td>1087</td>
<td>1.40</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ferraris et al., 1988¹²⁴</td>
<td></td>
<td>325</td>
<td>140</td>
<td>∞</td>
<td>1513 ± 978</td>
<td>1.6</td>
<td>3600</td>
<td>3.1</td>
</tr>
<tr>
<td>Kallis et al., 1994³¹</td>
<td></td>
<td>300</td>
<td>80</td>
<td>∞</td>
<td>1185</td>
<td>1.5</td>
<td>1620</td>
<td>1.7</td>
</tr>
<tr>
<td>Turpie et al., 1993¹¹³</td>
<td>Heart valve operation</td>
<td>100</td>
<td>5.4</td>
<td>0.5</td>
<td>—</td>
<td>—</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>McCollum et al., 1991¹¹⁶</td>
<td>Femoro-popliteal bypass</td>
<td>300</td>
<td>64</td>
<td>2.0</td>
<td>—</td>
<td>—</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sibai et al., 1993³⁴</td>
<td>Parturition</td>
<td>60</td>
<td></td>
<td>1.0</td>
<td></td>
<td>1.16</td>
<td>Haematoma</td>
<td>0.86</td>
</tr>
<tr>
<td>CLASP, 1994³³</td>
<td>Parturition (included 29% caesarian deliveries)</td>
<td>60</td>
<td>1.0</td>
<td>1.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage et al., 1988¹²⁵</td>
<td>Tonsillectomy</td>
<td>4000</td>
<td>Day 1—12</td>
<td>Days 2—9—31</td>
<td>Overall—43</td>
<td>—</td>
<td>42</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* Events/1000 patients treated. ** Total as given in publication or calculated from units of packed cells and fresh frozen plasma given. RRP, ratio relative to placebo.
Table 8  Bleeding events in aspirin-treated groups per 1000 patients undergoing major surgery (summarized from Appendices 1 and 2 of APTC 1994 Part III)

<table>
<thead>
<tr>
<th></th>
<th>Reoperation + haematoma + wound infection</th>
<th>Major bleeds not at operation site—fatal* or requiring transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials Patients Placebo Other All</td>
<td>Trials Patients Placebo Other All</td>
</tr>
<tr>
<td>Reoperation</td>
<td>22 2083 16 6 22 2083</td>
<td>41 3619 30 11 41 3619</td>
</tr>
<tr>
<td>Haematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>10 1517 85 0 80 20 2740 4.9 6 5.1</td>
<td></td>
</tr>
<tr>
<td>Orthopaedic trauma surgery</td>
<td>8 360 100 84 94 10 478 21 75 31</td>
<td></td>
</tr>
<tr>
<td>Orthopaedic elective surgery</td>
<td>4 206 49 No data 49 11 401 10 19 12</td>
<td></td>
</tr>
<tr>
<td>All surgery</td>
<td>83 80 80 80 80 7.5 18 9.1 2.84</td>
<td></td>
</tr>
<tr>
<td>Relative risk of events compared with placebo group</td>
<td>1.35</td>
<td>2.84</td>
</tr>
</tbody>
</table>

Placebo, placebo-controlled trials; Other, trials involving other antiplatelet agents as comparator; trials, number of trials providing data; patients, number of patients treated with aspirin. * Two fatal bleeds recorded in aspirin groups, none in control groups.
than indicated here. 77

12,74

for instance, Frith and Warlow

maximum factor of about 2.5. In some poor respond-

protective mucosal mucus-bicarbonate coat, by
technical variations in even the so-called standard ard, soluble, enteric coated or intravenous), and the

and found that many accepted statements have little and sometimes contradictory, particularly regarding

prolong bleeding time. Some investigators suspect and possibly causes—certainly exacerbates—peptic

ex vivo

and extension of skin bleeding time by a

1a
dozen prevent prostacyclin (measured as PGF

optimum dosage of drug in each individual. increases in microhaemorrhage from normal gut.

15

in a long-term treatment study. We need more tract.

79–84

in platelets.

79

oxygenase (COX–1) activity in vascular endothelium imal systemic bioavailability of aspirin

and non-responders, since improvement of the risk-

variation, but who may be representatives of distinct aggregation; inhibition of cytoprotective mucosal

appear to be ‘good’ and ‘poor’ responders, who possibly represent extremes of a wide inter-individual

but overlapping populations. In good responders,

whether normal volunteers or patients, a daily dose

of 40 mg or more causes, after 4 days, strong inhibition of collagen- or ADP-induced aggregation

ex vivo and extension of skin bleeding time by a

maximum factor of about 2.5. In some poor respond-

ers, 5–10-fold greater doses may be necessary to

prolong bleeding time. Some investigators suspect

that the dose-effect relation is less straightforward

than indicated here.12,74 Rodgers and Levin75 have

critically reviewed the literature on bleeding times,

and found that many accepted statements have little

factual support. Interpretation is bedevilled by the

technical variations in even the so-called standard

bleeding times,76 in addition to biological variation:

for instance, Frith and Warlow77 found no bleeding
time difference between aspirin- and placebo-takers

in a long-term treatment study. We need more information on the true status of apparent responders

and non-responders, since improvement of the risk-

benefit balance can only come about by using the

optimum dosage of drug in each individual.

There has been great interest in preserving cyclo-

oxygenase (COX–1) activity in vascular endothelium

and in the kidney,79 while obtaining full inhibition

in platelets.79–84 Limited success may have been

achieved with low doses, particularly in enteric

coated and controlled release formulations, and

perhaps with reduced dose frequency. However,

Kyrle et al.85 have shown that doses of ordinary

aspirin as low as 35 mg/day can at 2 h after last
dose prevent prostacyclin (measured as PGF1\(_2\)) pro-
duction in bleeding time incision blood, as well as

thromboxane production in both in clotting blood

and bleeding time incision blood (see also Preston

et al.86), such inhibition does not appear to be always
detectable by measuring urinary excretion of prosta-
cyclin end metabolites.87 Even though prostacyclin

production may recover quickly, the utility of the

concept of sparing prostacyclin production by use

of low doses of aspirin has still to be proven

experimentally and clinically. The relatively large

aspirin dose of 1200 mg/day is neither more nor less

effective in reducing thrombosis than currently

recommended regimens of 40–75 mg/day or every

other day.

**Gastrotoxicity**

Three mechanisms might lead to a causal relationship

between aspirin taking and increased gastrointestinal

microhaemorrhage, viz. inhibition of platelet aggregation; inhibition of cytoprotective mucosal

prostaglandin synthesis and physical damage to the

luminal surface of the mucosa. It is difficult to

separate the effects of these mechanisms. Platelet

aggregation is effectively inhibited by quite low doses

of aspirin, as noted above. Hawkey and coworkers15

have shown that a moderate dose of aspirin

(300 mg/day) effectively suppresses gastric mucosal

PGE\(_2\) production. Local physico-chemical irritation,

with or without suppression of the secretion of the

protective mucosal mucus-bicarbonate coat, by

aspirin (or other non-steroidal) gives rise to erosions,

and possibly causes—certainly exacerbates—peptic

duodenal ulcers,15,67–70,88–91 and accelerates the

shedding of mucosal cells into the gut lumen.92

Beyond these points, the literature is inconclusive

and sometimes contradictory, particularly regarding

the influences of aspirin dose and formulation (stand-

ard, soluble, enteric coated or intravenous), and the

presence of pre-existing gastrointestinal pathology

on the source, amount and time-course of blood shed-

ding into various segments of the gastrointestinal

tract.13,15,70,93–103

In summary, it appears that both an effect on

arachidonate metabolism and physical breakdown

of the mucosal protective layer are required for large

increases in microhaemorrhage from normal gut.15

Although controlled-release formulations give min-

imal systemic bioavailability of aspirin79 and may

reduce systemic effects on mucosal prostaglandin

synthesis, no oral presentation (except, perhaps,

sublingual104) can avoid local inhibition at the site

of uptake of the active drug through the gut wall.

Standard or soluble aspirin increases the frequency

of gastric erosions, but this is probably without

clinical significance: however, in the presence of

other predisposing factors (e.g. *H. pylori* infection),
aspirin may increase the likelihood that erosions

progress to peptic ulcers. Thus, aspirin increases
gastrointestinal haemorrhage largely only when major lesions or other pathology are present.

**Risk and benefit**

**Arterial disease**

Aspirin is an important drug which can reduce vascular mortality and morbidity. It is now standard clinical practice to use aspirin after acute myocardial infarction, when, in the short term, the risk of less than one bleeding episode of any kind is outweighed by approximately 40 major vascular events averted. The advantages in acute stroke management are smaller, but worthwhile. The reduction of all cause mortality by about 5 and of recurrent stroke by about 8 per 1000 patients treated must be balanced with an increase of about two haemorrhagic strokes and four major extracranial bleeds per 1000 patients.

The consensus from major clinical trials of aspirin concerning long-term use (Table 6) is that 1000 patients have to be treated for 1 year to prevent 15–20 fatal or non-fatal vascular events. Thus, it is very reasonable to recommend long-term dosing in high-risk patients, for whom there is an approximate trade-off of 5–7 major vascular events prevented, about one-third fatal, for every attributable major gastrointestinal bleed, which is most unlikely to be fatal.

The efficacy of, and indications for, a drug are determined by the absolute, rather than the proportional, number of clinical events avoided by its use. By this criterion, aspirin has an important role, since it reduces morbidity and mortality in vascular disease, which is common. In contrast, in people at low risk of vascular events, the balance of risk and benefit is even, fewer than one event being avoided for each major bleed. In the US physicians trial the increased risk of intracranial haemorrhage outweighed the very minor absolute benefit of reduction of myocardial infarction and stroke. The benefit was minor not because aspirin was less effective in giving a proportional reduction in vascular events, but because the population studied was at extremely low risk of developing vascular events. In such circumstances, it is probably not wise to recommend aspirin treatment for primary prevention.

**Surgery, deep-vein thromboses and pulmonary embolism**

There is evidence from overviews that pre-operative or immediate post-operative aspirin use may reduce significantly the rates of both early and late occlusion of vascular grafts. It may also reduce the risk of both post-operative deep vein thrombosis (by about 25%) and embolism (fatal plus non-fatal by about 60%). However, aspirin may also increase the need for re-operation to stop bleeding or to drain operation site haematomas. The balances of risk and benefit are close in all cases. Some authors have advocated stopping aspirin at least 5 days before elective operations so that the patient’s haemostatic mechanisms have returned to normal before operation: the gain in safety is balanced by exposure of the patient to possible thrombosis. On balance, we find no convincing argument either way, but feel it is likely that the excess rate of operation site complications attributable to aspirin is more than balanced by the reduction in thrombotic complications: we suggest that aspirin treatment is continued. There is no good evidence that aspirin use pre-operatively leads to any excess subdural bleeding when regional anaesthesia is used. A large trial, the Pulmonary Embolus Prevention (PEP) Trial is in progress to determine the balance of benefit (in preventing arterial and venous thrombosis) and risk (including haemorrhage) compared to placebo of 162 mg of enteric coated aspirin given daily from pre-operatively for 5 weeks in about 14 000 patients undergoing surgery for fractured neck of femur; the results are expected in early 1999.

**Perspective**

The clinical benefits of aspirin may be put into perspective by comparing it to fibrinolytic therapy after myocardial infarction, which is justifiably seen as a dramatic, life-saving treatment. The Fibrinolytic Therapy Trialists’ Collaborative Group, after reviewing all fibrinolysis trials of over 1000 patients concluded that an excess of 3.9 ± 0.8 strokes and 7.3 ± 0.7 major bleeds per 1000 patients treated was an acceptable trade-off for the 18 ± 3 deaths avoided in the immediate post-infarct period. The risk-benefit ratio for aspirin in long-term thromboprophylaxis estimated by Roderick, Wilkes and Meade appears even more favourable; between 0.2 and 8 attributable adverse events are offset by 2–10 deaths plus 4–20 serious non-fatal vascular events deferred per 1000 patient-years of exposure to any dose of aspirin. Of more importance, only a very small proportion of the attributable haemorrhagic events, specifically intracranial haemorrhage and severe gastrointestinal bleeding, are potentially disabling or fatal. Thus, the perception amongst clinicians, and the general public, that low-dose aspirin is an inexpensive and relatively harmless drug which provides meaningful benefits in reducing vascular disease is broadly correct. The use of low-dose aspirin is recommended for all groups of people with an increased risk of thrombosis.

**Conclusions**

Aspirin use significantly reduces the risk of vascular morbidity and death. Benefit can be obtained with
moderate (300 mg/day) or low (75 mg/day, perhaps even less) dose regimens. Risks of serious complications—intracranial or severe gastrointestinal or severe peri-operative haemorrhage—appear relatively constant between different patient groups, and do not appear to be diminished with lower dose regimens. The justification for use in a particular indication depends on the absolute risk of vascular morbidity and mortality. Aspirin use is fully justified in high-risk groups, defined by prior myocardial infarction, major or minor ischaemic stroke, or peripheral vascular occlusive disease. The putatively increased risks in other groups, such as diabetics, smokers, impaired exercise tolerance and more particularly the elderly as such, remain to be defined, and the utility of aspirin treatment determined for each. On the basis of balance of risk and benefit, use in subjects without a recognized risk factor for vascular disease is probably not justified.

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References

Assessing aspirin

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