

Controversies in cardiovascular medicine

Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither?

Carlo Patrono*

Department of Pharmacology, Catholic University School of Medicine, Largo Francesco Vito 1, 00168 Rome, Italy

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Low-dose aspirin has been shown to be effective in preventing about one-fifth of atherothrombotic vascular complications (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in a meta-analysis of 16 secondary prevention trials in patients with previous myocardial infarction, stroke, or transient cerebral ischaemia. This corresponds to an absolute reduction of about 10–20 per 1000 patients in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death. Against this benefit, the absolute increase in major extracranial bleeding complications [mostly, gastrointestinal (GI)] is 20- to 50-fold smaller, depending on age and sex. Hence, for secondary prevention, the benefits of antiplatelet therapy substantially exceed the risks. For primary prevention, the balance between vascular events avoided and major bleeds caused by aspirin is substantially uncertain because the risks without aspirin, and hence the absolute benefits of antiplatelet prophylaxis, are at least an order of magnitude lower than in secondary prevention. The aim of this article is to review the updated evidence for the efficacy and safety of low-dose aspirin in primary prevention and to discuss additional health benefits resulting from prolonged antiplatelet therapy in apparently healthy people at low average risk of vascular events.

Keywords

Aspirin • Primary prevention • Major vascular events • Major bleeding complications • Chemoprevention of cancer

Introduction

Low-dose aspirin has been shown to be effective in preventing about one-fifth of atherothrombotic vascular complications (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in a meta-analysis of 16 secondary prevention trials in patients with previous myocardial infarction, stroke, or transient cerebral ischaemia.¹ This corresponds to an absolute reduction of about 10–20 per 1000 patients in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death.¹ Against this benefit, the absolute increase in major extracranial bleeding complications [mostly, gastrointestinal (GI)] is 20- to 50-fold smaller, depending on age and sex.¹ Hence, for secondary prevention, the benefits of antiplatelet therapy substantially exceed the risks. Whether this favourable benefit/risk ratio extends beyond the 2–3 year duration of randomized treatment has not been formally tested. However, in patients prescribed with low-dose aspirin for the secondary prevention of cardiovascular or cerebrovascular events, discontinuation of antiplatelet therapy

was associated with a 40% increase in the relative risk of ischaemic stroke² and myocardial infarction³ compared with continuation of therapy.

For primary prevention, the balance between vascular events avoided and major bleeds caused by aspirin is substantially uncertain because the risks without aspirin, and hence the absolute benefits of antiplatelet prophylaxis, are at least an order of magnitude lower than in secondary prevention.¹ The aim of this article is to review the updated evidence for the efficacy and safety of low-dose aspirin in primary prevention and to discuss additional health benefits resulting from prolonged antiplatelet therapy in apparently healthy people at low average risk of vascular events.

Some mechanistic considerations to interpret clinical trial results

Before discussing the results of aspirin trials in primary prevention, it seems appropriate to review briefly the unique features of

* Corresponding author. Tel: +39 06 30154253, Fax: +39 06 3050159, Email: carlo.patrono@rm.unicatt.it

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aspirin's pharmacokinetics (PK) and pharmacodynamics (PD) in inhibiting platelet function.^{4,5} The drug permanently inactivates the cyclooxygenase (COX) activity of the platelet enzyme, prostaglandin (PG)G/H-synthase-1 (also referred to colloquially as COX-1), responsible for the first committed step in prostanoid biosynthesis. In human platelets, this results in dose- and time-dependent inhibition of thromboxane (TX)A₂ formation. Platelet TXA₂ production represents an important amplification mechanism of platelet activation, by virtue of its being triggered in response to any platelet agonist and in turn inducing further platelet recruitment and aggregation.⁶ In healthy subjects, inhibition of platelet TXA₂ production by aspirin is cumulative upon repeated daily dosing and saturable at low doses (≥ 30 mg) because of its irreversible nature.⁷ In contrast to the uniform effectiveness of low-dose aspirin in blocking platelet COX-1 activity in healthy individuals,⁸ some clinical conditions are associated with suboptimal antiplatelet effects of aspirin. These include patients following coronary artery bypass surgery,⁹ patients with essential thrombocythaemia,¹⁰ patients with coronary artery disease who have metabolic syndrome (independently of diabetes mellitus),¹¹ and type 2 diabetes mellitus.¹² The mechanisms of suboptimal aspirin effect in these conditions are likely related to the fact that they all are associated with increased *in vivo* platelet activation.⁶ Thus, impaired acetylation of platelet COX-1 could result from accelerated platelet turnover,¹⁰ or from platelet activation-induced generation of hydroperoxides that are known to impair the acetylation of COX-isozymes by aspirin.¹³ Given the short half-life (~ 20 min) of aspirin in the human circulation, the long-lasting duration of its antiplatelet effect is ensured by acetylation of COX-1 in bone-marrow megakaryocytes and limited *de novo* protein synthesis in blood platelets.^{4,5} These factors typically allow a once daily regimen of aspirin administration, when the drug is used as an antiplatelet agent. However, changes in the systemic bioavailability of the drug, as may occur with some enteric-coated formulations and in association with obesity,¹⁴ or faster renewal of the drug target, as may occur in association with altered megakaryopoiesis,¹⁵ may limit the duration of its antiplatelet effect and require a different (e.g. bid) dosing regimen.^{15,16}

As detailed in Table 1, the aspirin regimen in six of the nine primary prevention trials was a once daily regimen of 75 or 100 mg aspirin in enteric-coated or controlled-release formulations;^{17–22} one trial used a daily regimen of 500 mg;²³ and two US studies^{24,25} opted for alternate-day regimens of 100 or 325 mg. Rocca *et al.*¹⁶ have recently described substantial inter-individual variability in the recovery rate of platelet COX-1 activity during the 24 h dosing interval, in both diabetic and non-diabetic patients treated with enteric-coated 100 mg aspirin. When contrasting the effects of aspirin in primary vs. secondary prevention, it should be considered that the vast majority of secondary prevention trials utilized plain aspirin tablets, and about 70% of participants allocated to active treatment in these trials were randomized to bid, tid, or qid regimens of aspirin administration.¹ A variable combination of these factors may have contributed to small differences in the effect size of aspirin in primary vs. secondary prevention trials,¹ and explain the largely inconclusive findings of the most recent primary prevention trials.^{20–22} The PK/PD rationale of a 48 h dosing interval of aspirin administration in two

primary prevention studies^{24,25} has never been convincingly articulated. One should therefore entertain the possibility that inadequate platelet inhibition during the second half of the dosing interval may have reduced the effect size of the benefit of antiplatelet prophylaxis and the statistical power of the Physicians' Health Study (PHS)²⁴ and the Women's Health Study (WHS)²⁵ to demonstrate a significant reduction in their respective primary endpoints.

Randomized clinical trials of aspirin in primary prevention

Nine completed primary prevention trials are available. The design and eligibility criteria of these trials are detailed in Table 1. They recruited over 100 000 participants, with a mean duration of follow-up of 6 years. Over 4000 serious vascular events occurred during this time frame, with an average annual rate of $\sim 0.6\%$, ranging from as low as 0.25 to as high as 2.4% in the control arm (Figure 1). Some unusual characteristics of these trials are worth mentioning, because they help explain the current heterogeneity in the medical and regulatory positioning of low-dose aspirin in primary prevention. They were designed and implemented by academic groups of investigators, independently of an industrial development plan. This is reflected by the fact that they addressed widely different populations, at extremely variable cardiovascular risk as noted earlier, using different aspirin regimens, and with different primary endpoints [ranging from as hard as mortality in the PHS²⁴ to as soft as a mixed bag of 'atherosclerotic events' in the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial²¹]. As a consequence, no two such trials can be clearly identified yielding a consistent result in the same population of at-risk subjects, with the possible exception of the two studies in male English-speaking doctors,^{23,24} hardly a suitable criterion for a medical indication. Thus, it is not surprising that several regulatory authorities, including the Food and Drug Administration, have not approved an indication for aspirin in primary prevention. Some scientific organizations recommend primary antiplatelet prophylaxis in certain intermediate-risk clinical settings (e.g. diabetes mellitus)²⁶ or when the estimated 10-year cardiovascular risk is above a certain threshold.²⁷ The recently issued American College of Chest Physicians guidelines²⁸ suggest low-dose aspirin over no aspirin therapy for persons aged 50 or older without symptomatic cardiovascular disease, with no emphasis on patient characteristics, such as older age, sex, or diabetes mellitus. However, according to the 2012 European Guidelines on cardiovascular disease prevention in clinical practice,²⁹ aspirin cannot be recommended in primary prevention due to its increased risk of major bleeding.

So, why is aspirin used relatively liberally for primary prevention, particularly in certain countries (e.g. the USA), despite these regulatory constraints and medical uncertainties? I believe that the main reasons are at least two-fold. First, the results of individual trials have often been presented and interpreted largely focusing on the positive results in selected secondary endpoints (e.g. the reduction of myocardial infarction in men, or the reduction of ischaemic stroke in women), while neglecting the negative results on the primary endpoint of the study (i.e. mortality in the PHS²⁴ and

Table 1 Design and eligibility criteria of primary prevention aspirin trials

	Dates of recruitment	Participating countries	Year of main publication	Number of participants	Mean duration of follow-up (years)	Target population	Eligible age range (years) at entry	Aspirin regimen	Randomized factorial comparison	Placebo control
British Doctors' Study ²³	November 1978–November 1979	UK	1988	5139	5.6	Male doctors	19–90	500 mg daily	None	No
US Physicians' Health Study ²⁴	August 1981–April 1984	USA	1988	22 071	5.0	Male doctors	45–73	325 mg on alternate days	β-carotene vs. placebo	Yes
Thrombosis Prevention Trial ¹⁷	February 1989–May 1994	UK	1998	5085	6.7	Men with risk factors for CHD	45–69	75 mg daily	Warfarin vs. placebo	Yes
Hypertension Optimal Treatment Trial ¹⁸	October 1992–May 1994	Europe, North and South America, Asia	1998	18 790	3.8	Men and women with DBP 100–115 mmHg	50–80	75 mg daily	Three blood pressure regimens	Yes
Primary Prevention Project ¹⁹	June 1993–April 1998	Italy	2001	4495	3.7	Men and women with one or more risk factors for CHD	45–94	100 mg daily	Vitamin E vs. open control	No
Women's Health Study ²⁵	September 1992–May 1995	USA	2005	39876	10.0	Female health professionals	45 or older	100 mg on alternate days	Vitamin E vs. placebo	Yes
Prevention of Progression of Arterial Disease and Diabetes Trial ²⁰	November 1997–July 2001	UK	2008	1276	6.7	Men and women with type 1 or 2 diabetes and ABI ≤0.99	≥40	100 mg daily	Antioxidant vs. placebo	Yes
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Trial ²¹	December 2002–May 2005	Japan	2008	2539	4.4	Men and women with type 2 diabetes	30–85	81 or 100 mg daily	None	No
Aspirin for Asymptomatic Atherosclerosis Trial ²²	April 1998–December 2001	UK	2010	3350	8.2	Men and women with ABI ≤0.95	50–75	100 mg daily	None	Yes

major vascular events in the WHS,²⁵ respectively). Secondly, the results of several meta-analyses of these trials^{1,30,31} have been overinterpreted as providing proof of efficacy and safety of low-dose aspirin in primary prevention, rather than generating hypotheses on a realistic effect size to be tested in properly sized randomized trials.

The results of the Antithrombotic Trialists' (ATT) collaborative meta-analysis¹ of individual participant data from six randomized trials^{17–19,23–25} have been widely discussed during the past 4 years and are summarized in Table 2. Because three additional primary prevention trials have been published since its completion, i.e. POPADAD,²⁰ JPAD,²¹ and AAA,²² Table 2 also lists two more

recent meta-analyses^{30,31} of tabular data from the nine randomized trials. The main results of the latter do not materially change the picture portrayed by the ATT meta-analysis,¹ as the three more recent trials only contributed <10% of the overall information. One possible difference is represented by a marginally significant reduction in all-cause mortality in the updated meta-analyses^{30,31} that was not apparent in the ATT meta-analysis.¹ Overall, aspirin allocation yielded a 12% proportional reduction in major vascular events, due mainly to a reduction by about one-fifth in non-fatal myocardial infarction. This proportional benefit would translate into a number-needed-to-treat (NNT) of ~2000 low-risk individuals to prevent one non-fatal myocardial infarction. The apparent 5–6% proportional reduction in all-cause mortality would translate into an NNT in excess of 3000 to prevent one (largely non-vascular) death. However, as detailed in Table 2, the statistical uncertainty surrounding this point estimate is pretty substantial, and therefore it should only be considered indicative of the potential effect size to be tested in future studies.

Finally, in light of the point estimates reported in Table 2, it should be emphasized that even the PHS²⁴ and the WHS²⁵ were largely underpowered to demonstrate a realistic benefit in their primary endpoint, despite their large sample size and extended follow-up.

Clinical read-outs of platelet COX-1 inactivation

Platelets physiologically survey the integrity of the vascular endothelium.⁶ They also participate importantly in repair mechanisms following atherosclerotic plaque fissuring or rupture, or GI mucosal injury.⁶ Interference with these repair functions by anti-platelet therapy may be responsible for delayed healing and/or intra-lesion haemorrhage. However, putting a brake on platelet reactivity may also prevent pathological escalation of these repair functions into occlusive or proliferative responses affecting a major artery⁶ or a small segment of the GI mucosa.³² The following sections review the potential clinical read-outs of platelet COX-1 inactivation by low-dose aspirin.

Prevention of atherothrombosis: heart vs. brain

That low-dose aspirin prevents about one-quarter to one-fifth of major coronary events is both biologically plausible, given the pathophysiology of atherothrombosis,⁶ and convincingly demonstrated by the reduced risk of these events in aspirin-treated

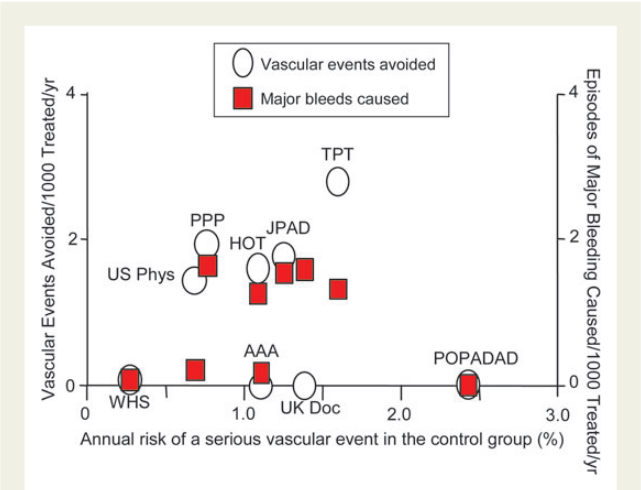


Figure 1 Benefits and risks of low-dose aspirin in primary prevention trials as a function of underlying cardiovascular risk. Vascular events (circles) avoided and major bleeds (squares) caused per 1000 treated with aspirin per year are plotted from individual aspirin trials in different patient populations characterized by variable cardiovascular risk, as noted on the abscissa. For each of the nine trials, a couple of symbols describe the absolute benefit (circles) and hazard (squares) associated with 1 year of aspirin therapy in 1000 subjects. WHS, Womens' Health Study; US Phys, US Physicians' Health Study; PPP, Primary Prevention Project; HOT, Hypertension Optimal Treatment; UK Doc, British Doctors Trial; TPT, Thrombosis Prevention Trial; POPADAD, Prevention Of Progression of Arterial Disease And Diabetes Trial; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; AAA, Aspirin for Asymptomatic Atherosclerosis Trial. Modified and updated from Patrono et al.⁴

Table 2 Meta-analyses of primary prevention aspirin trials

Meta-analysis	Major vascular events	Major coronary events	Any stroke	Vascular death	Any death
ATT Collaboration: ¹ rate ratio (95% CI)	0.88 (0.82–0.94)	0.82 (0.75–0.90)	0.95 (0.85–1.06)	0.97 (0.87–1.09)	0.95 (0.88–1.02)
Raju et al: ³⁰ relative risk (95% CI)	0.88 (0.83–0.94)	0.83 (0.69–1.00)	0.93 (0.82–1.05)	0.96 (0.84–1.09)	0.94 (0.88–1.00)
Bartolucci et al: ³¹ odds ratio (95% CI)	0.87 (0.80–0.93)	0.85 (0.69–1.02)	0.92 (0.83–1.02)	0.96 (0.80–1.14)	0.93 (0.87–1.00)

patients representing the whole spectrum of atherothrombosis, from apparently healthy, low-risk individuals¹ to patients with an acute myocardial infarction.³³ At least six placebo-controlled clinical trials with unequivocally positive results on the pre-specified primary endpoint of each trial have demonstrated a 23–51% relative risk reduction in both fatal and non-fatal coronary events in patients presenting with chronic stable angina,³⁴ unstable angina,^{35–38} or acute myocardial infarction.³³ These trials have spanned in duration from as short as 1 week³⁷ to as long as 50 months.³⁴ Moreover, they tested a wide range of daily doses of aspirin, from as low as 75 mg^{34,38} to as high as 1300 mg,³⁶ with apparent saturability of the antithrombotic effect at the lowest dose.³⁹ Although the effect size of the benefit of aspirin in preventing non-fatal myocardial infarction is quite consistent in both low-risk and high-risk trials, this is not apparently the case for the prevention of coronary deaths. While no obvious pathophysiological explanation can be offered for this apparent discrepancy, it should be emphasized that coronary deaths accounted for about one-third vs. 60% of major coronary events in primary prevention vs. secondary prevention trials, respectively.¹

That low-dose aspirin may prevent a somewhat smaller fraction of ischaemic strokes than coronary events is also biologically plausible, given the heterogeneity of mechanisms underlying cerebrovascular ischaemia.⁴⁰ The evidence supporting aspirin's efficacy and safety in patients with non-cardioembolic transient ischaemic attack or stroke is reflected by consistent class 1A recommendations

both for the acute treatment and its secondary prevention.⁴⁰ However, aspirin increases the risk of haemorrhagic stroke;¹ therefore, the overall effect on any stroke will depend on the balance between ischaemic and haemorrhagic strokes. While the overall balance is in favour of using aspirin for secondary prevention, given the relatively small proportion of haemorrhagic strokes in patients who have survived a first ischaemic stroke,¹ this is not the case in people without a prior cerebrovascular event in whom the proportion of haemorrhagic strokes is approximately four-fold larger (13 vs. 3%, respectively).¹

Rothwell *et al.*⁴¹ have recently performed additional analyses of six primary prevention trials of daily low-dose aspirin vs. control to examine the effects on major vascular events, incident cancer, and major extracranial bleeds after stratification by the period of follow-up (Figure 2). In contrast to cancer incidence, for which the effect of aspirin increased with duration of trial follow-up (see in what follows), the effects on major vascular events and major extracranial bleeds diminished with increasing follow-up, leaving only the reduced risk of cancer from 3 years onwards⁴¹ (Figure 2). Some time-related trends would be expected over several years of follow-up due to withdrawal from trial treatment in the aspirin groups and open use of aspirin in the placebo groups. It is also plausible that the non-significant trend for the reduction in vascular benefit depicted in Figure 2 reflects time-related reduction in the number of vascular events and loss of statistical power of the analyses.

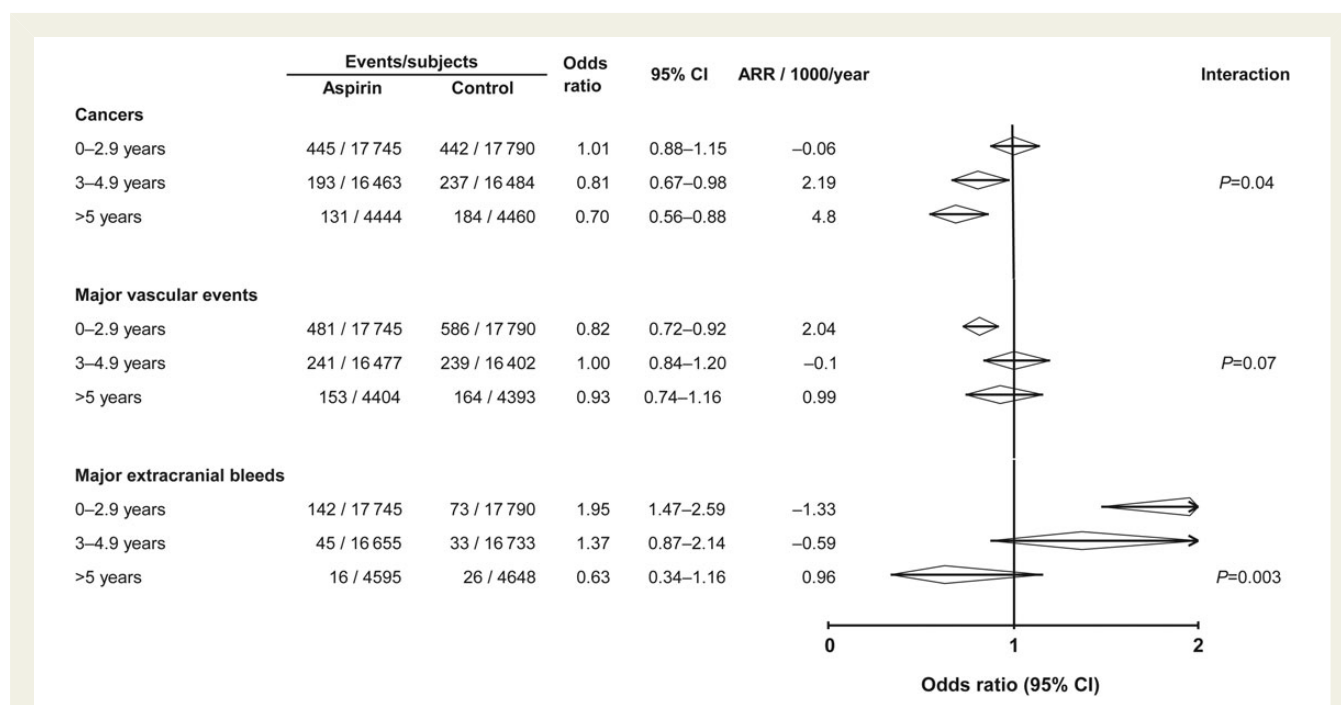


Figure 2 Summary of meta-analyses of the effect of aspirin on risks of incident cancer, major vascular events, and major extracranial bleeds during six randomized trials of daily low-dose aspirin vs. control in primary prevention of vascular events stratified by period of trial follow-up (0–2.9; 3–4.9; ≥5 years). The number of subjects at the start of each period is based on the number of individuals surviving free of the relevant outcome event at the start of the period, such that only first events of each type are included. ARR is absolute reduction in risk per 1000 participants per year. The statistical significance of the interaction between the treatment effect and the period of follow-up is derived from a Cox model in which the time is included as a continuous variable. Reproduced with permission from Rothwell *et al.*⁴¹

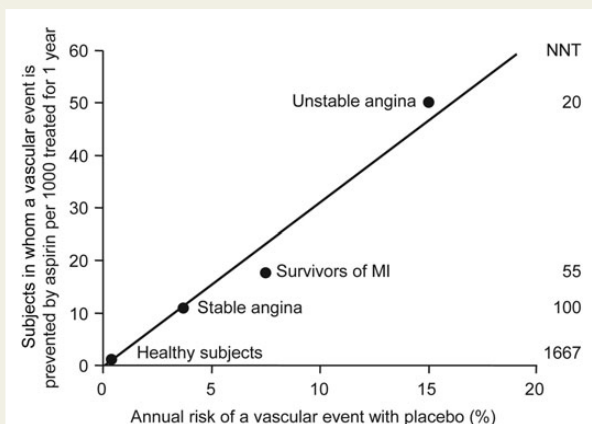


Figure 3 The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arm of the trial(s). The absolute benefit of antiplatelet treatment is reported on the ordinate as the number of subjects in whom an important vascular event (non-fatal myocardial infarction, non-fatal stroke, or vascular death) is prevented by treating 1000 subjects with aspirin for 1 year. Numbers needed to treat (NNT) to prevent one event in each clinical setting are also displayed on the right-hand side of the figure. Reproduced with permission from Patrono *et al.*⁵

Increased risk of bleeding: extracranial vs. intracranial

Aspirin does not cause a generalized bleeding abnormality unless it is given to patients with an underlying haemostatic defect, such as haemophilia, uraemia, or that induced by anticoagulant therapy.^{4,5} Aspirin-induced impairment of primary haemostasis cannot be separated from its antithrombotic effect, because both effects reflect suppression of TXA₂-dependent platelet function.⁴

The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic vs. haemorrhagic risk of the patient (Figures 3 and 4). Thus, in individuals at low risk for vascular occlusion (e.g. $\leq 1\%$ per year), a very small absolute benefit may be offset by exposure of a large number of healthy subjects to undue bleeding complications. In contrast, in patients at high risk of cardiovascular or cerebrovascular complications (e.g. $> 3\%$ per year), the absolute benefit of aspirin prophylaxis clearly outweighs the harm (Table 3). For example, the absolute excess of major bleeds (i.e. those requiring transfusion) in acute myocardial infarction is approximately one-hundredth the absolute number of major vascular events avoided by aspirin therapy.⁴² However, it should be emphasized that the balance described in Table 3 represents the best case scenario, inasmuch as people at high risk of bleeding complications, because of prior history of GI problems or advanced age, were either excluded from or underrepresented in randomized trials of antiplatelet therapy. As depicted in Figure 4, the number-needed-to-harm (NNH) for aspirin causing

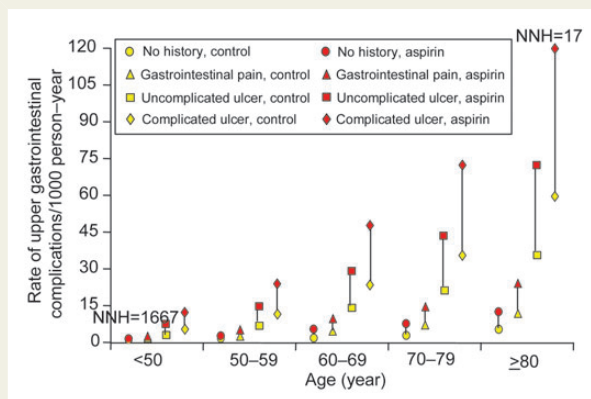


Figure 4 Estimated rates of upper gastrointestinal complications in men, according to age and the presence or absence of a history of such complications and regular treatment with low-dose aspirin. The solid lines connecting each pair of yellow and red symbols depict the absolute excess of complications related to aspirin therapy. UGIC, upper gastrointestinal complications; NNH, number-needed-to-harm. Reproduced with permission from Patrono *et al.*⁴

a major GI bleeding complication can vary ~ 100 -fold, depending on the prior GI history and the age of the patient. Other important risk factors for extracranial bleeds include diabetes mellitus, male gender, cigarette smoking, higher blood pressure, and body mass index.¹ In fact, with the notable exception of elevated blood cholesterol, the same risk factors appeared to predict major vascular events and major extracranial bleeds in the six primary prevention trials analysed by the ATT Collaboration.¹ This finding helps explain the apparent trend for a relationship between the underlying cardiovascular risk and the absolute excess of major bleedings due to aspirin, in the nine trials of people without symptomatic vascular disease (Figure 1). The same apparent trend is confirmed by analyses of individual participant data from six primary prevention trials in the ATT collaborative meta-analysis,¹ comparing the predicted 5-year absolute effects of allocation to aspirin on major vascular events and non-fatal GI or other extracranial bleeds in different categories of coronary heart disease risk (Figure 5).

Aspirin-induced GI complications, as detected in randomized clinical trials, appear to be dose related in the range of 30–1300 mg daily.⁴ This, along with studies of the relationship of efficacy to dose, is based largely on indirect comparisons of different trials and on a limited number of randomized, direct comparisons of different aspirin doses. Such a dose–response relationship is thought to reflect at least two COX-1-dependent components, i.e. dose-dependent inhibition of COX-1 in the GI mucosa and dose-independent (within the range of examined doses) inhibition of COX-1 in platelets.^{4,5} Therefore, it is not surprising that the antithrombotic effect of aspirin can be dissociated, at least in part, from its most common side-effect. However, even when administered at low doses, aspirin can cause serious GI bleeding, as reported in studies using 30–50 mg daily.^{43,44} Because of the underlying prevalence of gastric mucosal erosions or ulcers

Table 3 Benefit and harm of antiplatelet prophylaxis with aspirin in different settings

Clinical setting	Benefit ^a Number of patients in whom a major vascular event is avoided per 1000/year	Harm ^b Number of patients in whom a major GI bleeding event is caused per 1000/year
Men at low-to-high cardiovascular risk ^{17,23,24}	1–3	1–2
Essential hypertension ¹⁸	2	1–2
Chronic stable angina ³⁴	10	1–2
Prior myocardial infarction ⁴²	18	1–2
Unstable angina ^{35–38}	50	1–2

Modified from Patrono et al.⁵

^aBenefits are calculated from randomized trial data discussed in this review and depicted in Figure 3.

^bExcess of upper GI bleeding is estimated from a background rate of 1–2 events per 1000 per year in the general population of aspirin non-users and a relative risk of 2.0 associated with aspirin prophylaxis. Such an estimate assumes comparability of other risk factors for upper GI bleeding, such as age and concomitant use of NSAIDs, and may actually underestimate the absolute risk in an elderly population exposed to 'primary' prevention.

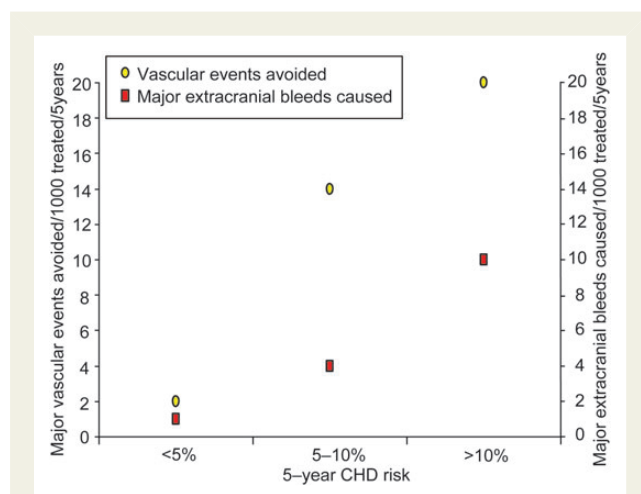


Figure 5 Predicted 5-year absolute effects of allocation to aspirin in avoiding major vascular events and causing major extracranial bleeds, in three different categories of calculated baseline 5-year risk of coronary heart disease (CHD). Data were calculated from the ATT collaborative meta-analysis of six primary prevention trials.¹

related to concurrent use of other NSAIDs and/or *Helicobacter pylori* infection in the general population, it should be expected that any antiplatelet agent will cause more bleeding from pre-existing lesions than a placebo. Consistent with this mechanistic interpretation, the relative risk of hospitalization due to upper GI bleeding associated with low-dose aspirin therapy (75–300 mg daily) was comparable to that of clopidogrel, i.e. 1.8 (95% CI, 1.6–2.0) vs. 1.7 (95% CI, 1.2–2.2), respectively, in a large cohort study with nested case–control analysis.⁴⁵ Similarly, in the recently completed PERFORM trial⁴⁶ in over 18 000 patients with a recent ischaemic stroke, the rates of major bleeding and GI bleeding were virtually identical in those treated with low-dose aspirin (100 mg daily) and those treated with terutroban, a TXA₂ receptor antagonist with no effect on COX-1-dependent GI cytoprotection. It should be emphasized that low-dose aspirin may increase the

risk of both upper and lower GI bleeding (A. Lanos, personal communication).

In the overview of the ATT Collaboration, information was available on 787 major extracranial haemorrhages in 60 trials recording at least one such haemorrhage.⁴² These were generally defined as haemorrhages that were fatal or required transfusion; among them, 159 (20%) caused death. Overall, the proportional increase in the risk of a major extracranial bleed with antiplatelet therapy was about one-half (odds ratio 1.6; 95% CI, 1.4 to 1.8), with no significant difference between the proportional increases observed in each of the five high-risk categories of patients. After allowing for non-compliance in the trials, these estimates are compatible with the two-fold excess observed in case–control studies.^{45,47}

As depicted in Figure 2, the odds ratio for major extracranial bleeds during six primary prevention trials of daily low-dose aspirin vs. control was ~2.0 during the first 3 years of follow-up, but diminished with prolonged follow-up.⁴¹ The apparent reduction in the effect of aspirin on risk of major extracranial bleeding events with increasing follow-up was due to a fall in risk in the aspirin group rather than to an increase in risk in the placebo group, and may be due, at least in part, to a fall in the proportion of susceptible individuals due to treatment withdrawal following a bleeding event, GI intolerance, or other side-effects.⁴¹

The widely held belief that enteric-coated and buffered formulations of aspirin are less likely to cause major upper GI bleeding than plain tablets was tested in data from a multicentre case–control study.⁴⁸ The relative risks of upper GI bleeding for plain, enteric-coated, and buffered aspirin at average daily doses of ≤325 mg were 2.6, 2.7, and 3.1, respectively. At doses >325 mg, the relative risk was 5.8 for plain and 7.0 for buffered aspirin; there were insufficient data to evaluate enteric-coated aspirin at this dose level.⁴⁸ Similar conclusions were reached by a case–control study using data from the UK General Practice Research Database.⁴⁹

Suppressing acid secretion is known to reduce the risk of ulcers associated with regular use of NSAIDs.^{5,50} In high-risk patients (history of previous ulcer bleeding) taking low-dose aspirin for 6 months, omeprazole and *H. pylori* eradication were associated with similar rates of recurrent bleeding (0.9 vs. 1.9%),⁵¹ although

clinically important differences between the two preventive strategies could not be excluded owing to the small sample size of the study. A recently completed case-control study suggests that while proton pump inhibitors are associated with decreased risk of upper GI bleeding they appear to increase the risk of lower GI bleeding (A. Lanas, personal communication).

Substantially less information is available concerning the risk of intracranial haemorrhage associated with aspirin use. In the overview of the ATT Collaboration,⁴² the overall absolute excess of intracranial haemorrhage due to aspirin therapy was <1 per 1000 patients per year in high-risk trials, with somewhat higher risks in patients with cerebrovascular disease. As noted earlier, the meta-analysis of primary prevention trials suggests that aspirin was associated with five additional haemorrhagic strokes per 1000 among moderate-risk participants (risk of coronary event >1% per year) over 5 years (i.e. ~1 out of 1000 per year), but substantially less than this among low-risk participants.¹

Chemoprevention of cancer

Despite suggestive evidence for a potential role of aspirin in cancer prevention, clinical guidelines for prophylactic use^{27–29} currently consider only the cardiovascular benefits of treatment and whether these outweigh the potential harm from aspirin-induced bleeding. Protection against colorectal cancer has been considered based on both case-control and cohort studies, but the absolute benefit from reducing the risk of this site alone was considered insufficient to justify treatment in average risk individuals, given the risk of bleeding.⁵² Until recently there has been no randomized evidence that regular aspirin use protects against any form of cancer and no attempt to integrate cancer prevention with the cardiovascular benefits of treatment. There have also been unresolved questions about the aspirin dose and treatment regimen needed for cancer prevention. In particular, it has seemed implausible that the low-dose regimen (75–100 mg once daily) recommended for cardioprotection could effectively inhibit carcinogenesis systemically through the mechanisms that had been proposed.⁵³

More recently, long-term follow-up of randomized trials of daily aspirin vs. control in cardiovascular prevention has shown that low-dose aspirin reduces the incidence and mortality due to colorectal cancer after a delay of 8–10 years,^{54,55} and reduces deaths due to several other common cancers after delays of 5–15 years.⁵⁶ The results were surprising in that the lowest doses used in these trials (75–100 mg once daily) appeared to be as effective as higher doses (300–1200 mg daily). Subsequently, a pooled analysis of six primary prevention trials of daily use of low-dose aspirin (75–100 mg) found a similar reduction (HR = 0.76; 95% CI, 0.66–0.88; $P = 0.0003$) in overall cancer incidence during follow-up occurring after 3 or more years on aspirin (Figure 2), and a reduction in total cancer mortality (HR = 0.63; 95% CI, 0.47–0.86; $P = 0.004$) from 5 years onwards.⁴¹ Interestingly, aspirin reduced cancer incidence in women as well as men.⁴¹

Some caveat in the interpretation of these findings should be mentioned. First, cancer incidence and mortality were not pre-specified endpoints of these cardiovascular trials. Secondly, the analyses by Rothwell et al.^{41,55,56} excluded the PHS²⁴ and WHS,²⁵ i.e. the two largest aspirin trials in which there is a lack of evidence of effects on cancer. Although the mechanistic

considerations discussed earlier may justify a separate analysis based on the 24 vs. 48 h dosing interval, this was a *post-hoc* separation that may be subject to bias. Moreover, no formal analysis has been presented that demonstrates statistical heterogeneity between the cancer results of aspirin trials of daily and alternate-day dosing.⁵³

The mechanism of the chemopreventive effect of aspirin and other NSAIDs against colorectal adenoma and cancer has long been related to shared inhibition of COX-2 activity in various cell types of the lower GI tract.⁵⁷ The main product of COX-2 activity in epithelial and stromal cells, PGE₂, has well-characterized effects in regulating apoptosis and cell proliferation.⁵⁷ Moreover, COX-2 gene deletion in mice and pharmacological inhibition of COX-2 activity in humans have been demonstrated to protect against the development or recurrence of both familial and sporadic colorectal adenomas.^{53,57} However, several experimental as well as clinical findings suggest the need to reconsider both the cellular and molecular targets of aspirin action. These include: (i) the demonstration that COX-1 gene deletion is just as protective as COX-2 knock-out in a murine model of genetically determined intestinal polyposis;⁵⁸ (ii) the results of four placebo-controlled randomized trials^{59–62} of aspirin, given once daily at doses as low as 81 mg, that suggest a largely similar chemopreventive effect against the recurrence of a sporadic colorectal adenoma as demonstrated with rofecoxib⁶³ or celecoxib⁶⁴; (iii) the fact that osteoarthritis patients taking aspirin 81 mg daily for 12 weeks did not have a significantly greater rate of gastroduodenal ulcers than patients given placebo⁶⁵ is consistent with the finding that stroke patients taking aspirin 100 mg daily for 2 years did not experience a higher rate of GI bleeding than patients treated with terutroban;⁴⁶ these observations provide indirect evidence that low-dose aspirin given once daily does not affect COX-1 (or COX-2) activity in the gastroduodenal mucosa to any clinically meaningful extent; (iv) the recent finding of Rothwell et al.^{55,56} of a chemopreventive effect of once-daily aspirin regimens, at doses as low as 75–100 mg, against overall cancer incidence and mortality. Thus, the chemopreventive effect of aspirin in humans appears to recapitulate the unique features of its antithrombotic effect, i.e. the adequacy of a 24 h dosing interval (despite a 15–20 min half-life of the drug in the human circulation), and saturability of the protective effect at low doses.^{4,5} This, in turn, could reflect a common mechanism of action of the drug in protecting against atherothrombosis and cancer,⁵³ i.e. permanent inactivation of platelet COX-1.³² This working hypothesis could be reconciled with the established role of COX-2 in colorectal carcinogenesis by postulating that activated platelets may induce COX-2 expression in adjacent nucleated cells (e.g. stromal cells) at sites of intestinal mucosal injury.⁵³ This hypothetical sequence would involve platelet signalling through paracrine soluble mediators of both lipid (e.g. prostanoids) and protein nature (e.g. growth factors and inflammatory cytokines), in turn inducing COX-2 expression and an eicosanoid amplification loop promoting cell proliferation and angiogenesis. A sequential involvement of COX-1 (in platelets) and COX-2 (in various nucleated cells) in the early events leading to the transformation of a 'normal' intestinal mucosa into an adenomatous lesion would explain the apparently similar impact of low-dose aspirin and COX-2 inhibitors in reducing the

recurrence rate of a sporadic colorectal adenoma over the first 3 years of treatment, and protecting against cancer development over 5–10 years.⁵³

Balance of benefits and risks

While the balance of vascular benefits and risk of major GI bleeding due to aspirin is clearly favourable in patients with established coronary or cerebrovascular disease and at average haemorrhagic risk (Table 3), such a balance is substantially uncertain in middle-aged people without symptomatic vascular disease, and will depend on the estimated annual risk of vascular vs. bleeding complications in the individual patient. It is important to consider that the two risks may track together as a function of common determinants (Figure 5). It has been argued that the size of the absolute benefit of aspirin could be halved by the cardiovascular risk reduction associated with the use of other effective preventive strategies (e.g. statin therapy),¹ virtually abolishing the difference between the number of vascular events avoided and major bleeds caused by aspirin (Figure 5). However, the same halving of the absolute excess of bleeding complications could be expected from the use of effective cytoprotective strategies (e.g. *H. pylori* eradication, proton pump inhibition).⁵⁰ The HEAT trial (*Helicobacter* Eradication Aspirin Trial) is currently testing the hypothesis that a 1-week course of *H. pylori* eradication in 10 000 *H. pylori*-positive patients using low-dose aspirin will halve the incidence of subsequent adjudicated peptic-ulcer bleeding that results in hospitalization. Moreover, the recent demonstration that low-dose aspirin reduces deaths due to cancer and overall incidence during trial follow-up suggests that there is a modest overall short-term benefit in primary prevention after taking into account all of the major outcomes.⁴¹ Taken with the previously reported reductions in post-trial cancer deaths,^{55,56} the demonstration of overall benefit from aspirin in the short-term adds to the case for long-term use of aspirin for cancer prevention in middle age.⁴¹ It has been argued that even a 10% reduction in overall cancer incidence from prophylactic aspirin treatment would tilt the balance of benefits and risks, and substantially broaden the indication for treatment in populations at average risk.⁵³

Conclusions

For secondary cardiovascular prevention, the net benefits of adding aspirin to other preventive measures would substantially exceed the bleeding hazards, irrespective of age and gender.^{66,67} In contrast, for many people without pre-existing vascular disease, the cardiovascular benefits of adding long-term aspirin to other, safer, forms of primary prevention (e.g. statins and anti-hypertensive drugs) are likely to be of similar magnitude as the hazards.¹ Four ongoing primary prevention trials may help assess the benefit/risk profile of low-dose aspirin in preventing multiple outcomes (including dementia and cancer) in ~50 000 participants at somewhat higher cardiovascular risk than in the earlier trials, because of diabetes mellitus (ASCEND⁶⁸ and ACCEPT-D),⁶⁹ advanced age (ASPREE),⁷⁰ or a cluster of risk factors (ARRIVE).⁷¹ Hence, the currently available trial results do not seem to justify general guidelines advocating²⁸ or discouraging²⁹ the routine use of aspirin in all apparently healthy individuals above a moderate

level of coronary risk, unless additional long-term benefits of aspirin therapy become firmly established.⁶⁵ In the meantime, clinical judgement as well as adequate knowledge of the available data may help the doctor–patient relationship in making a personalized choice after considering the different components of a complex equation that includes the patient's preferences and values.

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