CLINICAL INVESTIGATION

The risks and benefits of prophylactic aspirin in vascular disease and cancer

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Substantial evidence from randomized trials confirms benefit from aspirin in the secondary reduction of vascular disease but there is debate about its use in primary prevention. More recently, evidence from long-term follow up and other studies indicates a reduction in cancer by aspirin. The undesirable effects of aspirin include gastrointestinal bleeding and, rarely, cerebral bleeding. However, deaths from gastrointestinal bleeding attributable to aspirin appear not to be increased, suggesting that the bleeds provoked by aspirin are not the most serious. There is also suggestive, but limited, evidence that cerebral bleeds may occur only in the presence of uncontrolled hypertension. It is important that in considering the risk–benefit balance of aspirin prophylaxis from a public health point of view, reductions in vascular disease events and in cancer are considered together. Furthermore, low-dose aspirin is prophylaxis and not treatment, and so advice about aspirin should be given to subjects within the context of a healthy lifestyle to enable them to make informed decisions about the protection of their own health.

Keywords: aspirin • cancer prevention • cancer treatment • cerebral hemorrhage • colorectal cancer • gastric bleeding • stroke prevention • vascular disease prevention

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Aspirin (acetyl salicylic acid) is a simple salt of salicylic acid, and the history of salicylates goes back to antiquity. Most plants and herbs contain salicylates, and some of their medicinal effects depend upon these compounds. Hippocrates, the 'father of medicine' recommended a brew of willow leaves for the relief of pain in childbirth, and later, in 1763 the Rev. Edmund Stone reported to the President of the Royal Society that powdered willow bark had helped a number of his parishioners who had various agues [1]. It was however a technician working in a dye factory, who, in 1897, produced the first aspirin [2] and, to this day, aspirin is used as a highly effective treatment for pain and for fever.

In the 1960s, aspirin was shown to reduce the aggregation of blood platelets, a key element in thrombosis, and this led to a randomized controlled trial that showed a reduction in vascular deaths from aspirin [3]. This stimulated an interest and initiated a new phase in research on aspirin. The results of numerous randomized trials led to the use of aspirin in vascular disease protection and it was referred to as 'the first miracle drug' [4]. However, the story of aspirin continues and evidence from observational and randomized studies now give evidence of a substantial reduction in cancer [5–7].

This paper we summarizes the evidence on aspirin in vascular disease and cancer from a public health point of view, and calls for informed debate on the risks and benefits of the drug and on how it might best be handled within healthcare.

Aspirin & vascular disease

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On the basis of a number of extensive overviews of randomized trials [8–10], low-dose aspirin prophylaxis is now accepted for patients who have clinical evidence of vascular disease, together with subjects who have a raised vascular risk score. Thus, in secondary prevention, the number of patients necessary to treat to prevent one vascular disease event is approximately 26–40 [8]. It should be noted, however, that surveys have indicated that the uptake of prophylactic aspirin in such patients is less than desirable [11,12].

The most extensive overview of aspirin in primary vascular trials, based on nine trials, gives the odds ratio in all cardiovascular events as 0.87 (95% CI: 0.80–0.93) [13]. However, doubts about the use of aspirin prophylaxis in healthy older subjects focus on the fact that the number of vascular events likely to be prevented can be similar to the number of bleeding episodes likely to be precipitated [14,15]. Thus, the number needed to treat in primary prevention has been variously estimated at approximately 300 [10], 500 [14] and over 1000 [9], while the number necessary to harm is between approximately 500 at age 60 years [9], and approximately 150 at age 80 years [14]. Such evaluations, however, ignore the simultaneous reduction in cancer risk and are based on the assumption that a bleed can be equated with a heart attack or a stroke with regard to severity and sequelae, and clearly this can be challenged. Hence, a comment in one of the major overviews is apposite: "*…the alternative to primary prevention (by aspirin) is deferral until some evidence of occlusive disease is noted ... [but] the first manifestations of disease might be a disabling of fatal event*" [8]. Rothwell *et al.* add that the benefit of aspirin on cancer risk "*will tip the balance in favor of treatment*" of asymptomatic older subjects [5]. Therefore, as a recent editorial comments: "*a decision on whether or not a patient should take an aspirin requires a robust discussion of its benefits and harms … [and] the elicitation of patient preferences*" [16].

Aspirin & cancer

The first evidence suggestive of a reduction in cancer by aspirin was a serendipitous finding in an exploratory prospective study [17]. Later, results from animal studies showing an increase in survival and a reduction in metastases, together with laboratory evidence that aspirin enhances apoptosis and DNA mismatch repair, cellular mechanisms protective of cancer, increased expectations of benefit from aspirin [18].

The early suggestive evidence has now been supplemented by results from randomized trials. Analysis of individual patient data from long-term follow up of subjects in five randomized trials reported a significant reduction of the 20-year risk of colorectal cancer mortality (hazard ratio [HR]: 0.66; 95% CI: 0.51–0.85) in those who had taken aspirin for 5 years or more [6]. The estimate for all cancer deaths was a 44% reduction (HR: 0.66; 95% CI: 0.50–0.87) in a similar study of seven randomized trials and a non-significant 59% reduction of colorectal cancer deaths (HR: 0.41; 95% CI: 0.17–1.00) [5]. Yet another pooled analysis of 34 trials reported that fewer cancer deaths occurred in those taking daily aspirin than in controls (odds ratio [OR]: 0.85; 95% CI: 0.76–0.96). Further analysis by the duration of time from randomization to cancer death, confirmed that the protective effect of taking aspirin increases with increasing years of aspirin intake and that the effect becomes significant usually after 5 years of taking daily aspirin (OR: 0.63; 95% CI: 0.49–0.82) [19]. In addition, there is some evidence from randomized trials suggesting that aspirin reduces metastatic cancer spread [20].

An objection that in none of the trials included in these follow-up studies had cancer reduction been a prior hypothesis was answered by the finding of closely similar results in an *ad hoc* trial by Burn *et al.*, in which 861 high-risk patients were randomly assigned to 600 mg aspirin daily [7]. After 4.5 years, 48 subjects had developed colorectal cancer (HR: 0.63; 95% CI: 0.35–1.13), and in those who had completed 2 years aspirin prophylaxis there was a reduction (HR: 0.41; 95% CI: 0.19–0.86).

Two aspects of these trials are of special interest. First, it had been predicted, both on the basis of observational studies and studies of the cellular effects of aspirin, that at least 5–10 years of aspirin use may be required for protection to become apparent [21–23]. The data in these long-term studies give evidence of such a delay. Second, the trial by Burn *et al.* had been based on patients with Lynch syndrome [7]. These patients have a form of hereditary colorectal and other cancers consequent upon an error in DNA mismatch repair and laboratory studies have shown that this mechanism is greatly enhanced by aspirin [24].

The evidence of benefit is not, however, entirely consistent, and some demand further evidence before aspirin prophylaxis is widely recommended [25,26]. The most recent overview however reports a meta-analysis based on the follow ups of 23 trials, none of which were included in any of the other overviews. The overall relative risk of non-vascular death was 0.88 (95% CI: 0.81–0.96) and for cancer deaths the relative risk was 0.77 (95% CI: 0.63–0.95). The authors of this report find their results "*convincing … of a preventive role of low-dose aspirin in non-vascular deaths*" [27].

Finally, there is evidence suggestive of benefit from

aspirin used as an adjunct treatment of cancer. One of the follow-up studies already mentioned reported evidence from five randomized trials of a reduction in cancer metastases, and hence a reduction in cancer mortality [20]. More direct evidence comes from studies of the survival of patients with cancer who take, or are given, aspirin in addition to more usual treatments. A prospective study of 341 women with breast cancer within the US Nurses' Health Study found that aspirin taking was associated with a reduction in distal recurrence and breast cancer deaths (RR: 0.57; 95% CI: 0.39–0.82) [28]. Similarly, a prospective cohort study of 1279 subjects with colon cancer reported a 29% reduction in colon cancer deaths in those who took aspirin regularly (HR: 0.71; 95% CI: 0.53–0.95) [29] in comparison with non-aspirin users, and the reduction appeared to be greater in subjects with tumors that over-expressed COX-2 (HR: 0.39; 95% CI: 0.20–0.76). In a further small, placebo-controlled, randomized trial, the 5-year survival of patients who had undergone esophagectomy was significantly higher, by approximately 10%, among patients allocated to aspirin therapy than among patients who received placebo [30].

The risks of aspirin prophylaxis

One or two subjects each year in every 1000 taking low-dose aspirin are likely to experience a GI bleed attributable to the aspirin [8,31,32]. There is however good evidence from randomized trials that deaths from bleeding are not increased by aspirin, suggesting that the bleeds attributable to aspirin are not the more serious, life-threatening bleeds. Thus, in six primary aspirin vascular trials [33] there were four deaths per 100,000 subjects per year in subjects randomized to aspirin and five per 100,000 in subjects randomized to placebo [33,34]. The report of the Antithrombosis Trialists meta-analysis confirms this: *"…there were actually fewer fatal bleeds in participants allocated to aspirin than in the controls (nine vs twenty)"* [8], as do Rothwell *et al.* in their overview of 51 trials: *"…case–fatality from major extracranial bleeds was also lower on aspirin than on control (8/203 vs 15/132; OR: 0.32; 95% CI: 0.12–0.83; p = 0.009)"* [19]. Yet further reassurance on bleeding attributable to aspirin is shown in the same report that the risk of a bleed in subjects randomized to aspirin was 1.95 (95% CI: 1.47–2.59) in the first 3 years on aspirin; lower in the next 2 years (OR: 1.37; 95% CI: 0.87–2.14) and 5 years after randomization there was no significant excess (OR: 0.63; 95% CI: 0.34–1.16) [19]. It is possible of course that this reduction with time could be due to subjects who bled stopping the aspirin, or starting to take a proton pump inhibitor (PPI), so further evidence should be sought in other long-term cohort studies.

Although rare, cerebral bleeding attributable to aspirin is a very much more serious event. The relative risk of a hemorrhagic stroke has been estimated to be approximately 1.2–1.7 [8,31,35] and the absolute incidence of such a stroke attributable to aspirin appears to be around two or three per 10,000 subjects on aspirin per year [8,32,35].

A major risk factor for hemorrhagic stroke is blood pressure and in one trial the blood pressure is reported to have been 158 mmHg in nine subjects who experienced a hemorrhagic stroke, compared with 135 mmHg in those who did not experience a stroke [36]. The HOT trial was based upon patients with hypertension but received adequate antihypertensive treatment [37]. Although the incidence of hemorrhagic strokes was the same in 9399 subjects on aspirin (seven fatal and 12 non-fatal hemorrhage strokes) as in 9391 subjects on placebo (eight fatal, and 12 non-fatal hemorrhage strokes) the incidence of hemorrhagic stroke was high (~20 per 10,000 in 3.8 years, or about five per year) confirming the additional risk of cerebral bleeding in hypertensive patients. An overview of antiplatelet agents in hypertensive patients concluded that while the benefit of antiplatelet therapy in secondary prevention is many times greater than the harm, in primary prevention in subjects with elevated blood pressure the benefit is negated by an increase in major hemorrhage [38].

It would seem advisable therefore that the blood pressure of every person who decides to take aspirin long term is checked whether or not it meets the criteria set in recent guidelines: <150 mm Hg systolic and <90 mm Hg diastolic [39]. If the subject has evidence of vascular disease, then appropriate antihypertensive therapy should be given and daily aspirin advised. If there is no evidence of vascular disease, aspirin should not be recommended unless there is evidence of an increased risk of cancer that might 'tip the balance' in favour of aspirin prophylaxis.

Reducing the risk of aspirin

Although there is a large amount of literature on bleeding from aspirin, and several reviews [40–42], most of the reports on preventive measures are inconclusive and few studies have involved randomization. It seems unfortunate that the opportunity to test ways of reducing the risk of bleeding was not taken in any of the major vascular trials.

Most people can take low-dose aspirin without difficulty. Perhaps approximately 5% of subjects get stomach irritation and this may be reduced if the drug is taken either with food or with a glass of milk. Enteric

coated tablets are associated with a reduced prevalence of gastric discomfort and irritation but this preparation does not appear to reduce the risk of gastric bleeding [40]. Dispersible or soluble preparations are likely to be the most reasonable form for long-term use.

For subjects with current indigestion or a history of stomach trouble, a PPI taken along with the aspirin will reduce the risk of bleeding [43–45] and reduce the likelihood that small gastric lesions will progress to ulceration [46]. However, a recent study has detected an increased incidence of cardiovascular events in patients treated with a PPI along with aspirin, while those given an H_2R receptor blocker showed no such increase [47].

Although a number of studies have shown a reduction in bleeding from aspirin following treatment of infection by *Helicobacter pylori* [48], re-infection with this organism is common [49], and convincing evidence of long-term benefit from eradication is lacking [50].

For a number of reasons it would seem to be reasonable to advise that aspirin is taken at night. Platelet reactivity appears to be greatest in the early morning [51], the risk of myocardial infarction is highest in the morning and in the Health Physicians Study the reduction in vascular events by aspirin was found to be considerably greater on early morning infarctions than on those that occurred later in the day [52]. Furthermore, the levels of gastric repair proteins are said to be highest at night [53,54] and studies have also shown a lower ambulatory blood pressure in persons taking aspirin, but only in those who took it at night [55].

Two trials provide suggestive evidence that a calcium supplement, taken along with aspirin, may enhance the benefit of aspirin on colon polyp growth [56]. In one trial, subjects who had been randomly assigned to a calcium supplement and declared that they frequently took aspirin, had a 65% reduction of advanced colon adenoma (relative risk [RR]: 0.35; 95% CI: 0.13–0.96) while in the other trial, subjects who had been randomized to aspirin and were also taking calcium supplements, had an 80% reduction in polyp growth (RR: 0.20; 95% CI: 0.05–0.81).

This suggestive finding needs to be replicated and yet, dietary calcium, and in particular the consumption of milk, has been shown to be associated with a reduction in colon cancer [57]. Although it has never been tested, it would seem highly reasonable to recommend that prophylactic aspirin is taken at night, together with a glass of milk. A glass of milk contains about 350 mg calcium and although this is less than the 1200 mg calcium supplement shown to enhance the effect of aspirin on colon adenomas [56], it might increase the anticancer effect of the aspirin and would probably reduce gastric irritation from the aspirin.

None of the above measures have been tested against the risk of cerebral hemorrhage from aspirin, and it seems that little is known as to how this outcome can be reduced, other than by ensuring that blood pressure, if raised, is adequately treated.

Finally, the natural response to a gastrointestinal bleed is to stop taking aspirin. This risks a rebound in vascular events, with estimates of the relative risk in an overview of 1.82 (95% CI: 1.52, 2.18) [58]. The wisdom of stopping aspirin prophylaxis has been more seriously challenged in a small randomized study in which 156 patients who had suffered a bleed while on low-dose aspirin were all given a PPI and were then randomized to aspirin again or to a placebo [59]. Recurrent bleeding occurred in 10.3% of the subjects on aspirin and in only 5.4% on placebo, but all-cause mortality was only 1.3% in those put back on aspirin but was 10.3% in those on placebo, leading to a HR for death in the subjects randomized back to aspirin of 0.2 (95% CI: 0.05–0.90). This work requires replication, but it stimulated an editorial with the title: "Aspirin withdrawal in acute peptic ulcer bleeding: are we harming patients?" [60].

So who should take prophylactic aspirin?

On the basis of vascular risk alone, recommendations have been made [61,62], and challenged [14] that regular aspirin taking be considered by men over the age of approximately 50 years, and by women over the age of approximately 55 years. Since little or no reduction in cancer is likely from low-dose aspirin until after at least 5 years of prophylaxis, prophylaxis has been recommended from approximately the age of 45 years [5]. On the other hand, there seems to be no evidence upon which an upper limit for prophylaxis could be fixed, and it seems unfortunate that estimates of the likely risks and benefits in people of advanced years have to be based on the results of trials that included mainly younger people and relatively few elderly subjects.

Patients with diabetes are at increased risk of vascular disease and they have an increased risk of colorectal cancer [63]. Low-dose aspirin should therefore be considered. However, on the basis that an inadequate inhibition of thromboxane in diabetes, and possibly in aspirin 'resistance', can be completely corrected by 100 mg aspirin twice daily [64], this should clearly be the dose advised while awaiting evidence from randomized trials.

Both the long-term follow-up studies [6,20] and the *ad hoc* trial in patients with Lynch syndrome

[7] gave evidence suggestive of a high effectiveness of aspirin in the reduction of colon cancer, possibly with a reduction of approximately 60% in lesions in the proximal colon (HR: 0.24; 95% CI: 0.11–0.52) [6]. These patients should be given advice about aspirin prophylaxis, together with other subjects with a strong family history of cancer. Colorectal screening by colonoscopy or by flexible sigmoidoscope has however been introduced in many countries and this not only reduces colorectal mortality by approximately 25% [65–67] but also detects and removes prevalent neoplastic lesions [68]. It would seem that a reasonable procedure would be to give information on the risks and benefits of aspirin – for both vascular events and for cancer – to all subjects offered colorectal screening. This would ensure that the subjects who decline screening, at present approximately 50% [68], and in particular those whose fecal occult blood test is positive but refuse colonoscopy, would be given information on another protective strategy.

Social & public health issues

McKee and Raine have pointed out with reference to choices about health: "first choose your philosophy" [69]. Prophylactic aspirin is not a treatment and if clinical advice is sought, or given, this should be within the context of health-related behaviours, and in particular non-smoking and regular exercise, so that people are enabled to make informed decisions about the protection of their own health.

Lenaghan *et al.* have urged that decision makers at a local and national level should take time and make an effort to obtain informed comment from groups representative of the general public, and should not only listen to, but should act on, the voice of the public [70]. A Citizens' Jury was conducted a few years ago under the title: 'My Health – whose responsibility?' and low-dose aspirin was used as an example of a protective medicine [71]. A total of 16 jurors, who had been chosen by stratified sampling in order to represent the general public, agreed that public money should be spent on informing people about the risks and benefits of low-dose aspirin. Although at the time of the jury (2006) the available evidence on the reduction of cancer by aspirin was not at its current level, the jurors stated that evidence on the risks and possible benefits relevant to cancer should be made available to the public even before there is agreement amongst doctors.

Conclusion

The cost of the treatment of vascular disease in the UK was estimated to be about GB£29 billion in 2004, and is responsible for about 20% of the total healthcare costs to the UK NHS [72], while the cost of cancer care was about £18.3 billion in 2008 [101]. Low-dose aspirin prophylaxis is already highly cost-effective for vascular disease [73,101] and, together with colorectal screening, aspirin seems likely to prove highly cost-effective in colorectal, and probably other cancers. Further studies on possible ways to reduce aspirin-related bleeding, and in particular cerebral bleeding, should be conducted as a matter of urgency.

Whether or not aspirin prophylaxis should be promoted for certain defined high-risk groups, or more generally, awaits guidance from the regulatory authorities.

Future perspective

At present a substantial proportion of older adults appear to be taking aspirin regularly, and this is likely to increase steadily. No regulatory authority has yet approved aspirin for cancer prevention, but this is likely to come, and it is hoped that wide discussions will first be held on how prophylactic aspirin is to be handled within healthcare. The prophylactic use

Executive summary

- From a public-health point of view, and for the individual patient, the benefits of low-dose aspirin prophylaxis on vascular disease and on cancer should be considered together.
- Daily low-dose aspirin (up to 100 mg daily) reduces vascular disease events by approximately 20–30% and it reduces cancer overall by approximately 30%. Reduction in vascular disease is immediate but there is a 5–10 year delay before a reduction in cancer becomes clinically apparent.
- There is highly suggestive evidence that aspirin, additional to conventional treatment, reduces metastatic spread of cancer and increases survival in a number of cancers.
- Aspirin increases the risk of gastrointestinal bleeding, the absolute risk being 2–3 per 1000 per year and increases the risk of hemorrhagic stroke by about 2–3 per 10,000 per year.
- There appears to be no increase in fatal gastrointestinal bleeds from aspirin, provided subjects with gastric pathology are excluded. Careful consideration of the risk–benefit balance from aspirin prophylaxis should be given to subjects with hypertension.
- There is an urgent need for widespread discussions, including the involvement of the general public, about how prophylactic aspirin should best be handled within healthcare.

of aspirin is limited by its undesirable side effects and it may be that natural salicylates in plant-based foods could be an adequate substitute for the drug. Preliminary studies on natural salicylates are promising, but much work is required, not least on acceptable ways of increasing the salicylate content of plant foods.

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