Is aspirin useful in primary prevention?

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There is no evidence that aspirin is effective for the primary prevention of cardiovascular events, although it may change the way that they present. Indeed, there is no evidence that long-term aspirin should be given to patients even with known cardiovascular disease. Theoretical arguments that aspirin can prevent cardiovascular events by reducing the propagation of thrombus are countered by evidence that plaque haemorrhage from vasa vasorum may also cause plaque growth and instability. There is evidence that aspirin causes serious bleeding into the brain and the gut. Aspirin may also detract from the benefits of drugs that have definite cardiovascular benefits, such as angiotensin-converting enzyme inhibitors. Meta-analysis is prone to multiple biases in favour of aspirin, including publication bias, bias due to trial and endpoint selection and bias due to interpretation. Meta-analysis should not be relied on in preference to adequately powered clinical trials. Unfortunately, the benefits of aspirin, if they exist, may be so small that a very large study indeed would be required to demonstrate that its benefits outweigh its risks. The evidence that aspirin might reduce cancer is intriguing but relies on data from trials conducted many decades ago using a wide range of aspirin doses. There is no reliable evidence that aspirin used in the current fashionable doses of 50–100 mg/day is of any benefit in any common clinical setting.

Keywords
Aspirin • Primary prevention

Is aspirin useful in primary prevention? Two further questions immediately spring to mind. Useful for the prevention of what? What about secondary prevention? The primary focus of this article is whether aspirin is useful for the primary prevention of acute coronary syndromes and stroke but will touch upon some other relevant questions.

So, is aspirin useful for the primary prevention of cardiovascular disease? The short answer is no! A slightly longer answer is that evidence of benefit is lacking for primary prevention and, if benefit does exist, may not outweigh harm. Analysis of recent studies is neutral for both non-fatal and fatal events (Figure 1). The small and uncertain benefits of aspirin reported in the twentieth century may now be surplus to requirements due to advances in treatment such as statins and good control of hypertension. Indeed, aspirin may detract from the benefits of drugs that are known to reduce cardiovascular risk, such as angiotensin-converting enzyme (ACE) inhibitors and possibly beta-blockers. Chronic aspirin therapy might once have been useful, although this has never been demonstrated, but may have been made redundant by more effective interventions.

Why then, in the absence of evidence, do so many people advocate the use of aspirin for primary prevention? There are four likely reasons. A belief that cardiovascular events are driven predominantly by thrombosis, deception by publication bias, choice of endpoint in clinical trials, and extrapolation from secondary prevention. Aspirin use is also associated with hearing loss and age-related macular degeneration, which might account for why some aspirin evangelists are unable to follow the scientific arguments proposed by those who take a more critical view of the evidence.

A traditional view of the trigger for a cardiovascular event is that the fibrous cap of an atheromatous lesion ruptures leading to thrombosis and that prevention of the propagation of thrombus will prevent evolution into full vascular occlusion. Plaque rupture exposes highly pro-thrombotic material and aspirin alone may have a limited effect. Indeed, the ineffectiveness of aspirin for preventing thrombus propagation has triggered a vast research effort into more effective agents. But why consider only one side of the coin? Atheroma is associated with the in-growth of fragile capillaries (vasa vasorum) from the adventitia. Much of the lipid from foam cells may be derived from red cell membranes and plaque haemorrhage, which may be exacerbated by anti-thrombotic agents, contributing both to the progression of atheroma and plaque instability (Figure 2). If plaque haemorrhage accounts for a substantial proportion of cardiovascular events then giving anti-thrombotic agents might be
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of cases/ participants, aspirin</th>
<th>No. of cases/ participants, placebo</th>
<th>Odds ratio (95% CI)</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>9</td>
<td>699/52145</td>
<td>841/50476</td>
<td>0.80 (0.67–0.96)</td>
<td>62.1% (21.7%–81.6%)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>9</td>
<td>326/52145</td>
<td>263/50476</td>
<td>1.06 (0.83–1.37)</td>
<td>37.4% (0.0%–71.2%)</td>
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<tr>
<td>Total CHD</td>
<td>9</td>
<td>1044/52145</td>
<td>1125/50476</td>
<td>0.88 (0.74–1.01)</td>
<td>68.4% (28.1%–82.7%)</td>
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<tr>
<td>Stroke</td>
<td>9</td>
<td>749/52145</td>
<td>755/50476</td>
<td>0.94 (0.84–1.06)</td>
<td>14.8% (0.0%–56.9%)</td>
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<tr>
<td>Total CVD events</td>
<td>9</td>
<td>2107/52145</td>
<td>2171/50476</td>
<td>0.90 (0.85–0.96)</td>
<td>0.0% (0.0%–55.4%)</td>
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<tr>
<td>CVD mortality</td>
<td>9</td>
<td>674/52145</td>
<td>611/50476</td>
<td>0.99 (0.85–1.15)</td>
<td>36.1% (0.0%–70.6%)</td>
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<td>Non-CVD mortality</td>
<td>9</td>
<td>1276/52145</td>
<td>1311/50476</td>
<td>0.92 (0.85–1.00)</td>
<td>0.0% (0.0%–4.2%)</td>
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<td>Cancer mortality</td>
<td>8</td>
<td>750/49919</td>
<td>762/48207</td>
<td>0.93 (0.84–1.03)</td>
<td>0.0% (0.0%–49.4%)</td>
</tr>
<tr>
<td>Noncancer, nonvascular mortality</td>
<td>8</td>
<td>481/49919</td>
<td>502/48207</td>
<td>0.90 (0.7601–1)</td>
<td>32.1% (0.0%–69.9%)</td>
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<tr>
<td>All-cause mortality</td>
<td>9</td>
<td>1962/52145</td>
<td>1933/50476</td>
<td>0.94 (0.88–1.00)</td>
<td>0.0% (0.0%–0.0%)</td>
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<tr>
<td>Total bleeds</td>
<td>9</td>
<td>22297/50868</td>
<td>18415/49208</td>
<td>1.70 (1.17–2.46)</td>
<td>98.2% (97.3%–98.5%)</td>
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<td>Nontrivial bleeds</td>
<td>9</td>
<td>5337/50868</td>
<td>4712/49208</td>
<td>1.31 (1.14–1.50)</td>
<td>65.7% (30.3%–83.1%)</td>
</tr>
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</table>

**Figure 1** Meta-analysis of the effects of aspirin on various outcomes in primary prevention trials (adapted from Seshasai et al.⁴⁰) with inset showing the evaporation of effect on non-fatal myocardial infarction in more recent trials reporting since the advent of widespread angiotensin-converting enzyme inhibitor and statin use.

**Figure 2** The main theoretical argument for aspirin is that it reduces platelet aggregation and prevents propagation of thrombus. However, aspirin may promote adhesion of platelets and possibly monocytes to the endothelium and aggravate thrombus formation and plaque growth. Also, micro-haemorrhage from fragile capillary neo-vascularization from vasa vasorum may destabilize plaque promoting plaque growth and/or rupture. It is likely that aspirin is sometimes beneficial and sometimes harmful, but that the overall effect on cardiovascular events is fairly neutral apart from the few weeks after an acute myocardial infarction. Aspirin may change the presentation of events (more sudden death and fewer patients presenting with classical cardiac pain) rather than their number.
unwise. Cardiovascular events are probably caused by a mixture of plaque haemorrhage and rupture with thrombosis and the proportions of each may vary depending on the clinical setting, which will determine the net benefit or harm of an agent such as aspirin. It should not be assumed that net benefit in one clinical setting will be observed in another. Aspirin may also inhibit new vessel formation, which may account for its purported effect on the development on cancers and could reduce new vessel formation in plaque, although it might not be so good for the damaged heart. However, aspirin does not appear to influence diabetes or hypertension.

Aspirin is a non-selective cyclo-oxygenase inhibitor. It blocks the production of thromboxane in platelets thereby inhibiting their aggregation but is also blocks the synthesis of prostaglandins in the vascular wall that, in health, causes vasorelaxation, maintains renal function, and reduces adhesion of platelets to the vessel wall (Figure 2). The ability of aspirin to reduce platelet aggregation will depend greatly on the local context. There is no evidence that reducing the dose of aspirin to 50–100 mg/day will spare vascular wall prostaglandin synthesis. Studies showing that lower doses of aspirin have similar effects to higher doses may be best interpreted as showing that neither dose is effective. Aspirin use is associated with an increased risk of dyspepsia, gastrointestinal bleeding, chronic kidney disease, renal dialysis and haemorrhagic stroke, and possibly deafness and age-related macular degeneration! In summary, the theoretical arguments can be bent in favour of or against aspirin depending on biases in opinion, but the simple fact remains that the evidence is uncertain and not a good basis for making clinical decisions for the health of billions of people alive today and in the decades to come. Clinicians are often forced to make decisions based on limited evidence, but should have the wisdom to distinguish between opinions and scientific evidence. We should not misrepresent opinions as facts, either to ourselves, to our colleagues or to our patients. Although we may recommend aspirin based on guesswork today, we should not resign ourselves to always having to do so. We must hope and strive for better evidence.

Next, we come to the thorny issue of biases in publication. This takes many forms. Small, outrageously positive studies get published but small studies that do not confirm the aspirin hypothesis are either never submitted for publication or suffer multiple rejections by editors and may never see the light of day. A registry of trials and a journal dedicated to publishing under-powered neutral studies is essential for a society addicted to meta-analysis, although very difficult to police for generic therapies such as aspirin. Meta-analysis is intrinsically biased towards positive results and must be considered second-best evidence. Meta-analysis should preferably only be used to confirm that the results of adequately powered studies are consistent with the rest of the literature or to define the size and duration of a definitive study to test the hypothesis created by the meta-analysis.

Many of the published studies of aspirin have a peculiar similarity in that they were clearly neutral but published as having a positive result. It is alarming that editors of journals as outstanding as the Lancet and New England Journal of Medicine allowed this to happen in the past; doubtless it would not happen today. The most outrageous example is the US Physicians’ Health Study. This study was stopped by its data monitoring committee for futility and yet published as a positive result. The primary endpoint of the study was all-cause mortality, which was almost identical in the aspirin and placebo groups. The authors chose, in retrospect, to re-focus on fatal and non-fatal myocardial infarction, excluding sudden deaths which were almost doubled in patients taking aspirin. They reported a substantial 44% reduction in fatal and non-fatal myocardial infarction. However, the total number of fatal myocardial infarctions and sudden deaths was similar in the aspirin and placebo groups. There was a trend to an increased rate of strokes, a recurrent feature of primary prevention trials. What drove the positive result of the reconstructed primary outcome was a large reduction in non-fatal myocardial infarction. Why did such a large reduction in non-fatal events not translate into a reduction in cardiovascular deaths for what was and remains a deadly disease? The 28-day case-fatality associated with myocardial infarction is reported to be ~40%, with the great majority of deaths occurring before the patient reaches hospital. Moreover, 25% of myocardial infarctions or even the majority are clinically ‘silent’ and unrecognized myocardial infarction carries an adverse prognosis. Could aspirin have changed the presentation of acute coronary syndrome rather than its true rate? The Hypertension Optimal Treatment (HOT) study may provide an answer. This study showed no benefit from aspirin on its original primary endpoint which was all fatal or non-fatal myocardial infarctions or strokes and no reduction in mortality. However, after retrospectively excluding patients with clinically silent myocardial infarctions, which were more numerous in those taking aspirin, a small reduction in events of borderline statistical significance was reported and, inappropriately, reported as the main conclusion of the paper. These two studies suggest that aspirin may change the presentation of myocardial infarction rather than preventing it. Aspirin may conceal rather than prevent myocardial infarction either by increasing the proportion of sudden deaths or reducing the number that are recognized. This could account for a reduction in clinically overt non-fatal events in those taking aspirin, without a commensurate reduction in mortality or myocardial damage. Any agent that was truly effective in reducing myocardial infarction should reduce cardiovascular mortality. For primary prevention, aspirin does not.

Meta-analyses of primary prevention have also consistently failed to include trials conducted primarily to examine the effects of aspirin on non-arterial disease. These patients are not immune to cardiovascular events. Studies of the prevention of colon cancer have suggested an excess of myocardial infarction and stroke with aspirin, while a large study of aspirin for the prevention of pulmonary embolism showed a significant increase in fatal and non-fatal myocardial infarction. Despite exclusion of these trials and biased reporting, recent meta-analyses have suggested no reduction in cardiovascular deaths with aspirin. Given the inherent bias of meta-analysis towards a positive result this reinforces the need for a definitive study to show that long-term benefit outweighs harm.
Even if an optimistic view of the cardiovascular benefits of aspirin is taken, the total health economic cost is not attractive at up to £62 000 per event prevented. Another line of argument is that aspirin is an effective agent for secondary prevention after the onset of coronary or cerebral vascular disease. However, there is evidence of publication bias in the long-term trials of aspirin after myocardial infarction, with the results of meta-analysis being driven by smaller studies (Figure 3). Large, long-term studies show neutral outcomes or trends to harm. Moreover, very few studies have been conducted with contemporary doses of aspirin. The lowest dose used in any long-term placebo-controlled study after myocardial infarction was 300 mg/day, and the only positive study showing a benefit from aspirin after myocardial infarction lasted just 1 month and used aspirin 162.5 mg/day. Newer anti-thrombotic agents have not been rigorously tested on top of doses of aspirin that are known to be effective, in the short term, compared with placebo. Dual anti-platelet therapy may not be required after an acute coronary syndrome when the dose of aspirin is > 100 mg/day. Current clinical practice with aspirin after myocardial infarction is not evidence based. Also, the short-term effects of aspirin after a stroke do not appear to translate into a reduction in either mortality or disability by 6 months. Guidelines on stroke now advocate use of clopidogrel monotherapy (less intensive therapy) rather than combination with aspirin, due to the increased risk of haemorrhage without a reduction in vascular events. A detailed discussion of the anti-platelet agents in the context of coronary stent placement is beyond the scope of this article, but there is a paucity of information on both the intensity and duration required. Recent evidence suggests that 6 months of dual anti-platelet therapy may suffice but perhaps 1 month would be enough. Whether any long-term anti-platelet agent is required after the coronary lesions have endothelialized has not been tested. Although a post hoc analysis of one large study suggested that the benefits of the anti-platelet agent ticagrelor may increase over time, whether persistent treatment was required to generate this effect cannot be determined due to the study design that lacked an early withdrawal arm. Moreover, ticagrelor may exert

**Figure 3** Publication bias plot of large, long-term trials of aspirin after myocardial infarction. Note that the meta-analysis is driven by small, outrageously positive trials and that large trials suggest a neutral outcome (adapted from Cleland).
benefits through mechanisms other than platelet inhibition, such as adenosine release. In summary, compared with a strategy of short-term aspirin prophylaxis, there is no evidence that long-term aspirin use in patients who have experienced a non-fatal cardiovascular event translates into a reduction in chronic morbidity, disability, or mortality.

There is only one compelling study showing benefit in patients after a myocardial infarction and that is International Study of Infarct Survival (ISIS)-2. In this study, 17,187 patients with an acute myocardial infarction were randomized, double-blind, to 162.5 mg of aspirin daily for 4 weeks or to placebo. It showed substantial benefit. In the previous ISIS-1 study that had investigated the use of i.v. atenolol during an acute myocardial infarction, only 5% of patients were discharged on an anti-platelet agent. The ISIS-2 investigators must have agreed there was no compelling evidence to use aspirin otherwise they would not have agreed to randomize patients to placebo. What happened after 4 weeks of double-blind treatment? Did investigators subsequently give aspirin? Surely not, as this was not their practice in ISIS-1 and could not be their practice if they were willing to randomize patients to placebo. We do not know for sure but in all probability aspirin was stopped after 4 weeks and yet the benefits of aspirin persisted for years after the trials conclusion. Some smaller observational studies may have suggested an excess of events on withdrawing aspirin, but there are too many confounding factors to draw any reliable conclusions from them.

Figure 4  Mortality (A) in the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment, SOLVD-Prevention and the risk of the composite of death, myocardial infarction or stroke in the Heart Outcomes Prevention Evaluation (HOPE) Trials (adapted from Cleland et al.). Note that in each case the benefit of the angiotensin-converting enzyme inhibitor was less, often markedly so, in patients taking aspirin. In HOPE, ~75% of patients were taking aspirin. This rose to >90% in the European trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) and The Prevention of Events with Angiotensin-Converting-Enzyme inhibition (PEACE) Trial with attenuation (EUROPA) and eventual loss (PEACE) of the effects of angiotensin-converting enzyme inhibitors (B adapted from Dagenais et al.). (B) The effect of angiotensin-converting enzyme inhibitors (ramipril, perindopril, and trandolapril) on death, non-fatal myocardial infarction, or stroke. All statistical P-values shown are tests for interaction. Strong interactions observed in multiple clinical trials are uncommon and unlikely to be due to the play of chance.
Moreover, trials of aspirin after myocardial infarction suggest that the greater the delay in initiating aspirin the smaller the benefit. It is possible that when plaque has ruptured, resulting in a coronary ‘溃疡’, which is a focus for thrombus generation with already obliterated anti-thrombotic defences and where plaque haemorrhage is irrelevant, aspirin becomes a ‘sword with but a single edge’ aimed at inhibiting thrombus propagation. However, once the acute event is over and the ‘溃疡’ has healed, any reduction in platelet aggregation by aspirin may be offset by inhibition of prostaglandin-mediated vascular wall defences and the increased risk of vasa vasorum capillary plaque haemorrhage.

Just as the hypothesis that aspirin is useful for the prevention of cardiovascular events is being laid to rest the hypothesis that it may prevent bowel and possibly other cancers is rising. One hypothesis is that aspirin prevents vascular proliferation in nascent tumours preventing their growth. This may or may not be a good thing for ischaemic hearts or brains. However, the data are far from conclusive. The data have been collected retrospectively from cardiovascular trials, the difference in the number of cancers (~100) is relatively small given the volume of data and loss to follow-up may have biased the result. Most of the effect occurred after the trials were complete and randomized medicine had been stopped. Trials of aspirin aimed at patients at risk of developing colon cancer showed an increase in cardiovascular events and no convincing reduction in tumours.

Aspirin increases the risk of cerebral and gastro-intestinal haemorrhage and this is associated with a striking increase in mortality in patients with cardiovascular disease. Cerebral haemorrhage often results in disabling or fatal stroke. Bleeding from peptic ulcers among older patients is associated with a high fatality. There are many explanations for this observation. It may be that both aspirin and ACE inhibitors interfere with prostaglandin metabolism and the effect of this on outcomes is less than additive (a bit like giving two ACE inhibitors). However, it is more likely that ACE inhibitors mediate a large part of their benefit by increasing vascular prostaglandin synthesis and that this is inhibited by aspirin.

Perhaps, the time for sterile argument is over. What we need is a definitive, modern trial of aspirin for primary prevention. Perhaps, this might be confined to those already taking statins—since this is both a group at an increased risk of events and one that has consented to taking regular medication. The study would need to be large, perhaps enrolling >30,000 people, and last at least 5 years. Aspirin sceptics have an open mind but do the aspirin evangelists?

Conflict of interest: J.G.F.C. has received a grant to investigate the effects of aspirin compared to clopidogrel on mortality amongst patients with heart failure.

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