Aspirin for primary prevention of cardiovascular disease?

Cardiovascular disease (CVD) is a leading cause of mortality.\(^1\) For example, in 2000, it accounted directly for around 2 million deaths in the European Union.\(^2\) Worldwide, many people take aspirin daily in the belief that doing so helps to prevent CVD. This approach is established for the secondary prevention of recurrent vascular events.\(^3,4,5\) However, there has been some uncertainty about the place of aspirin for the primary prevention of cardiovascular events.\(^6\) In particular, there have been doubts about whether any benefits of aspirin in people with no history of CVD outweigh the risks (e.g. the fact that long-term low-dose aspirin therapy almost doubles the likelihood of gastrointestinal haemorrhage\(^7,8\)). Here we consider the place of low-dose aspirin in primary prevention of CVD.

Guidelines on primary prevention

Various guidelines (published between 2005 and 2008) have recommended aspirin for the primary prevention of CVD in various groups of patients\(^1,3,8\) (an unlicensed indication in the UK).\(^10\)

A guideline from the National Institute for Health and Clinical Excellence (NICE) published in 2008 recommends that, for patients with type 2 diabetes mellitus, aspirin 75mg daily should be offered to those aged at least 50 years if their blood pressure is below 145/90mmHg, and to younger patients with other significant cardiovascular risk factors (e.g. smoking, hypertension).\(^9\)

Guidance from the Scottish Intercollegiate Guideline Network (SIGN) states that asymptomatic individuals without established atherosclerotic disease, but with a calculated cardiovascular risk of 20% or more over 10 years, should be considered for treatment with aspirin 75mg daily; it also states that patients with hypertension with the same 10-year risk should receive aspirin, but only once their blood pressure has been treated to below 150/90mmHg.\(^6\) SIGN currently also recommends aspirin 75mg daily for all people with type 2 diabetes aged over 50 years, and for selected younger individuals with diabetes who are considered to be at increased cardiovascular risk.

The Fourth Joint Taskforce of the European Society of Cardiology guidelines, published in 2007, recommend aspirin 75mg daily for asymptomatic individuals if their 10-year risk of CVD mortality is over 10% and blood pressure is controlled as closely as possible to the goal of less than 140/90mmHg.\(^1,11\) The Joint British Societies’ 2005 guidance recommends aspirin 75mg daily for all people aged over 50 years who have a total CVD risk of 20% or more over 10 years, and in selected people with diabetes (i.e. those aged at least 50 years, or younger patients who have had the disease for over 10 years, or who are already receiving treatment for hypertension), once blood pressure has been controlled to below 150/90mmHg.\(^5\)

Evidence on aspirin in primary prevention

Evidence prior to the guidelines

A meta-analysis (published in 2002) included 195 randomised trials of aspirin alone (or another antiplatelet regimen) versus a control and involved a total of 135,640 patients at high risk of occlusive vascular events (i.e. over about 2% per year).\(^2\) Most patients had already had one vascular event, but others had not and, consequently, the overall results of the analysis were extrapolated by some observers as indicating the potential benefits of aspirin in primary prevention. The analysis found that 7,705 serious vascular events had been recorded among 71,912 patients allocated to antiplatelet therapy compared with an adjusted total of 9,502 among 72,139 allocated to control treatment (10.7% vs. 13.2%, p<0.0001).\(^1\) However, more of the patients receiving antiplatelet treatment experienced major extracranial bleeding (1.13% vs. 0.71%; odds ratio [OR] 1.6, 95% CI 1.4 to 1.8). The findings led the reviewers to recommend that aspirin 75–150mg daily (or some other effective antiplatelet regimen) be considered routinely for all patients at high or intermediate risk of occlusive vascular events (more than about 2% per year), including those with an acute myocardial infarction or acute stroke and those with a previous infarction, or stroke or transient ischaemic attack, and also some groups of patients who had not had a major cardiovascular event (e.g. those with stable angina, atrial fibrillation, peripheral arterial disease). The reviewers pointed out “an unanswered question, however, is whether it is possible to identify particular groups of apparently healthy people who may be at increased risk of myocardial infarction or stroke and for whom the benefits of daily aspirin outweigh the hazards”.

Four meta-analyses,\(^12-15\) which all looked specifically at aspirin (dose range from 75–659mg daily) for primary prevention of CVD, included either four\(^13\) or five\(^12,14,15\) of six key trials.\(^16-21\)

In one meta-analysis, the reviewers suggested that, because of an equivocal effect in terms of reducing the likelihood of myocardial infarction, aspirin for primary prevention would most benefit people at “special risk” for myocardial infarction, such as those with diabetes.\(^12\)

In another meta-analysis, the reviewers concluded that aspirin was safe and worthwhile at a coronary event risk of 1.5% or more per year, of limited value at a risk of 1% per year and unsafe at a risk of 0.5% per year, meaning that aspirin could not be prescribed safely for primary prevention without formal estimation of the coronary event risk of the individual person.\(^19\)
In a third meta-analysis, the reviewers concluded that aspirin appeared to help prevent non-fatal myocardial infarction but increased the likelihood of gastrointestinal bleeding and possibly haemorrhagic stroke.14

In a fourth meta-analysis, the reviewers concluded that the evidence provided strong support that aspirin reduces the risk of a first myocardial infarction in apparently healthy individuals, but that consideration of whether to use the treatment for such benefits should also include assessment of the person’s 10-year risk of having a first coronary event and the likelihood of unwanted effects with long-term aspirin use.15

Direct evidence in hypertension
One systematic review pooled data from five randomised controlled trials assessing the use of antiplatelet agents in people with hypertension (blood pressure generally at least 160/100mmHg) for primary and secondary prevention.26 It included people with elevations of both systolic and diastolic blood pressure, or with isolated elevations of either systolic or diastolic blood pressure, and it addressed the following hypothesis: antiplatelet agents reduce total deaths and/or major thrombotic events when compared to placebo or other active treatment. The reviewers concluded that aspirin did not reduce the likelihood of stroke or “all cardiovascular events” compared to placebo in patients with elevated blood pressure and no prior CVD. In one large trial19 (involving 19,193 low-risk patients) included in the review, aspirin taken for 5 years reduced the likelihood of myocardial infarction (absolute risk reduction 0.5%, number needed to treat [NNT] 200 for 5 years), but also increased the likelihood of major haemorrhage (absolute risk increase 0.65%, number needed to harm [NNH] 154 for 5 years), and did not reduce cardiovascular mortality or all-cause mortality. The reviewers concluded that aspirin cannot be recommended for primary prevention in patients with elevated blood pressure because the magnitude of benefit is similar to the magnitude of harm.

Direct evidence in diabetes
A randomised controlled trial10 included in one of the meta-analyses discussed above12 compared aspirin (650mg daily) and placebo for the early treatment of diabetic retinopathy in 3,711 patients, around half of whom had no history of CVD. There was no difference between the two groups in mortality from all causes (the primary outcome measure for assessing the systemic effects of aspirin) or in cardiovascular mortality, in fatal or non-fatal myocardial infarction, or fatal or non-fatal stroke. The reviewers concluded that treatment, rate ratio 0.88, 95% CI 0.82 to 0.94; p=0.0001). This was due mainly to an absolute reduction of about 0.05% in the likelihood of non-fatal myocardial infarction (0.18% per year vs. 0.23% per year, p<0.0001; NNT per year around 2,000). Aspirin increased the likelihood of having major gastrointestinal or other extracranial bleeding (absolute risk increase of about 0.03% per year; 0.10% per year vs. 0.07% per year; relative risk [RR] 1.54 95% CI 1.30 to 1.82; p<0.0001; NNH per year around 3,300). The rates of all-cause mortality, of death due to coronary heart disease and of stroke did not differ between the aspirin and the control groups. The proportional reduction in serious vascular events did not depend significantly on age, gender, blood pressure, history of diabetes or predicted risk of coronary heart disease. The reviewers concluded that, with aspirin for primary prevention “the net absolute reduction in disabling or fatal occlusive events is likely to be small, and at least partially offset by a small increase in serious intracranial and extracranial bleeds”. They commented that currently available trials did not seem to justify general guidelines advocating the routine use of aspirin in all apparently healthy individuals with a more than moderate risk of coronary heart disease.

Effects according to gender
In a gender-specific meta-analysis, which included the same six primary prevention trials17-21,23 as the analysis discussed above,4 aspirin was associated with a decrease in major cardiovascular events in both women and men.24 Based on the absolute risk reduction during the trials (mean follow-up of 6.4 years) of 0.30% in women (OR 0.88, 95% CI 0.79 to 0.99; p=0.03) and 0.37% in men (OR 0.86, 95% CI 0.78 to 0.94; p=0.01), the NNT to prevent 1 cardiovascular event during 6.4 years of follow-up was 333 women and 270 men, respectively. In women, aspirin was associated with a reduction in the overall occurrence of stroke (OR 0.83, 95% CI 0.70 to 0.97; p=0.02; NNT 411) and in ischaemic stroke (OR 0.76, 95% CI 0.63 to 0.93; p=0.008; NNT 419), but not haemorrhagic stroke (p=0.89), myocardial infarction (p=0.95), cardiovascular mortality (p=0.56) or all-cause mortality (p=0.62). In men, aspirin was associated with a reduction in myocardial infarction (OR 0.68, 95% CI 0.54 to 0.86; p=0.001; NNT 118), but not overall stroke (p=0.14) or ischaemic stroke (p=0.98); and there was an increase in the occurrence of haemorrhagic stroke (OR 1.69, 95% CI 1.04 to 2.73; p=0.03). Also, in men, aspirin had no effect on cardiovascular mortality (p=0.87) or all-cause mortality (p=0.15). Aspirin therapy increased the risk of major bleeding in both women (absolute risk increase 0.25%, NNH over 6.4 years for 1 major bleeding event 400; OR 1.68, 95% CI 1.13 to 2.52; p=0.01) and men (absolute risk increase 0.33%, NNH 303; OR 1.72, 95% CI 1.35 to 2.20; p<0.001).

The reviewers concluded that treatment with aspirin for a mean of 6.4 years resulted in an average absolute benefit of around 3 cardiovascular events prevented per 1,000 women and 4 cardiovascular events prevented per 1,000 men. However, this was offset by an additional 2.5 major bleeding events per 1,000 women and 3 major bleeding events per 1,000 men.
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**Patients with diabetes**

Two recently published randomised controlled trials specifically investigated the use of aspirin for primary prevention in people with diabetes.\(^{25,26}\)

One of the trials, based in Scotland, was double-blind and included 1,276 people aged 40 years or more with type 1 or type 2 diabetes plus asymptomatic peripheral arterial disease as detected by a lower than normal ankle brachial pressure index (at most 0.99; a reading that would not usually trigger intervention), but no symptomatic CVD.\(^{25}\) After a median follow-up of 6.7 years, compared with ‘no aspirin’, aspirin 100mg daily had not reduced the proportion of people experiencing the following two composite primary end points: death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischaemia (18.2% with aspirin vs. 18.3% with no aspirin; hazard ratio [HR] 0.98, 95% CI 0.76 to 1.25; p=0.86); and death from coronary heart disease or stroke (HR 1.23, 95% CI 0.79 to 1.93, p=0.36).

The other trial, based in Japan, was non-blinded and involved 2,539 patients with type 2 diabetes without a history of atherosclerotic events.\(^{26}\) At a median follow-up of 2.5 years, compared with no aspirin (81mg or 100mg daily) or to no aspirin.\(^{26}\) At a median follow-up of 6.7 years, compared with ‘no aspirin’, aspirin 100mg daily had not reduced the proportion of people experiencing the following two composite primary end points: death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischaemia (18.2% with aspirin vs. 18.3% with no aspirin; hazard ratio [HR] 0.98, 95% CI 0.76 to 1.25; p=0.86); and death from coronary heart disease or stroke (HR 1.23, 95% CI 0.79 to 1.93, p=0.36).

The other trial, based in Japan, was non-blinded and involved 2,539 patients with type 2 diabetes without a history of atherosclerotic disease who were randomised to low-dose aspirin (81mg or 100mg daily) or to no aspirin.\(^{26}\) At a median of 4.37 years, there was no difference between the two groups in the primary outcome of all atherothrombotic events.

**Implications for practice**

Overall, we believe that the currently available evidence does not justify the routine use of low-dose aspirin for the primary prevention of CVD in apparently healthy individuals, including those with elevated blood pressure or diabetes; this is because of the potential risk of serious bleeds and lack of effect on mortality. Recent advice from the Medicines and Healthcare products Regulatory Agency has recommended that, if aspirin is used in primary prevention, “the balance of benefits and risks should be considered for each individual, particularly the presence of risk factors for vascular disease… and the risk of gastrointestinal bleeding.”\(^{26}\) In practice, this means reviewing individually all those patients currently taking aspirin for primary prevention (either as prescribed or over-the-counter treatment), with the decision to stop or continue treatment being made with the patients after fully informing them of the available evidence. Furthermore, in our view, current evidence makes it hard to recommend restarting aspirin for primary prevention.

**Conclusion**

Low-dose aspirin is established in the secondary prevention of cardiovascular disease. Such treatment is also widely used for the primary prevention of cardiovascular disease (an unlicensed indication). However, current evidence for primary prevention suggests the benefits and harms of aspirin in this setting may be more finely balanced than previously thought, even in individuals estimated to be at high risk of experiencing cardiovascular events, including those with diabetes or elevated blood pressure. We believe, therefore, that low-dose aspirin prophylaxis should not be routinely initiated for primary prevention. With respect to those people already taking low-dose aspirin for primary prevention, the decision about whether to continue with the treatment should be taken by both the patient and a healthcare professional in light of the available evidence. This also includes people who purchase aspirin over the counter for primary prevention.
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DOI: 10.1136/dtb.2009.0045