Aspirin and the primary prevention of cardiovascular disease

The benefits of using aspirin for preventing secondary cardiovascular events are well documented, but how confident are we that the benefits outweigh the risks of adverse consequences when given as primary prevention? To help answer this question Peter Burrill evaluates the evidence for and against the use of aspirin in the prevention of primary cardiovascular events.

Introduction

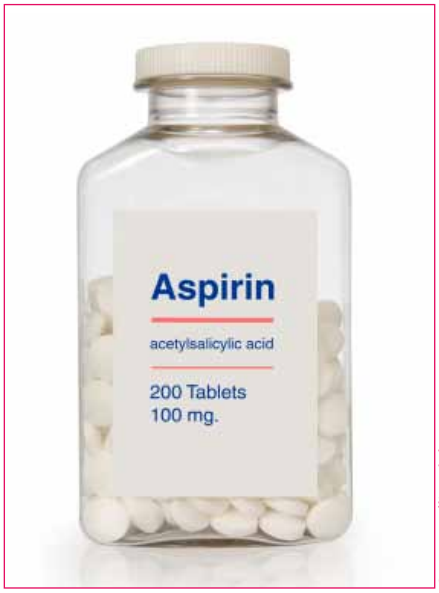
The antithrombotic trialists' collaboration (ATC) meta-analysis[1] showed that for those with previous myocardial infarction (MI), unstable or stable angina, stroke or cerebral ischaemia, peripheral arterial disease (PAD), or atrial fibrillation, low-dose aspirin was effective at reducing the risk of a vascular event. Although there is good evidence that aspirin is effective for secondary prevention of cardiovascular (CV) events what is the evidence for its effectiveness in *primary* prevention of CV events in high risk groups?

Diabetes

Several guidelines, including the National Institute for Health and Clinical Excellence (NICE) *Clinical guideline 66*,[2] recommend giving low-dose aspirin to people with diabetes for primary prevention. But is this based more on extrapolation of data from other high-risk groups rather than on direct evidence obtained from people with diabetes? The ATC meta-analysis, based on 4,961 people with diabetes in nine trials, did not show any benefit. A recent review found no convincing evidence that aspirin is effective for primary prevention in people with diabetes.[3] The authors commented: 'We can't always accept a practice as being evidence based even if it is advocated by most of our colleagues and endorsed by well renowned guidelines.'

Findings from the prevention of progression of arterial disease and diabetes (POPADAD) trial[4] were recently published and became headline news in the national press. The POPADAD study investigators recruited in Scotland people aged 40 years or more with type 1 or type 2 diabetes plus asymptomatic PAD but no symptomatic CV disease. After a median length of follow-up of 6.7 years no benefit was shown for aspirin over placebo.

An editorial about the POPADAD trial findings concluded: 'A total of seven well controlled trials now show that aspirin has no benefit for primary prevention of cardiovascular events, even in people at higher risk. Although aspirin is cheap and universally available, practitioners and authors of guidelines need to heed the evidence that aspirin should be prescribed only in patients with established symptomatic cardiovascular disease.'[5]



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The National Prescribing Centre (NPC) blog on this study suggested: 'For primary prevention in patients with diabetes mellitus, clinicians and patients should weigh this new evidence in their discussions. Some patients, perhaps especially those taking a large number of medicines, may wish to slightly simplify their medicines regimen and no longer take aspirin for primary prevention. The publication of this study has highlighted that evidence is accumulating that aspirin does not reduce future CV events in any group of patients who do not have existing CV disease.'[6]

POPADAD was closely followed by the JPAD trial.[7] This RCT involved 2,539 patients in Japan with type 2 diabetes without a history of atherosclerotic disease. Again there was no difference in outcomes between those who took aspirin and those who did not. These two recent studies can be criticised as being potentially underpowered, but the bottom line is that there appears to be no direct evidence that aspirin reduces risk in primary prevention in people with diabetes. Actually, a growing body of evidence suggests that diabetes could represent a special case of aspirin resistance.[8] There may be a good reason for aspirin being ineffective for primary prevention in this population.[9] With an atherothrombotic event, clot is formed and ruptured plaque is a huge stimulus for platelet aggregation. However, in primary

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prevention, where there has been no event, thrombus is not routinely formed.[9]

Hypertension

The *British National Formulary* (*BNF*, 57) recommendations are for 'long-term use of aspirin 75mg daily by patients with a 10-year CV disease risk of 20% or more and aged over 50 years'. Is there evidence for this indication?

Cochrane have conducted a systematic review[10] of the role of antiplatelet therapy and anticoagulation in patients with raised blood pressure. The review included people with elevations of both systolic and diastolic blood pressure, or isolated elevations of either systolic or diastolic blood pressure to address the following hypotheses: (i) antiplatelet agents reduce total deaths and/or major thrombotic events when compared to placebo or other active treatment; and (ii) oral anticoagulants reduce total deaths and/or major thromboembolic events when compared to placebo or other active treatment.

Aspirin (Acetylsalicylic Acid; ASA) did not reduce stroke or 'all CV events' compared to placebo in primary prevention patients who had elevated blood pressure and no previous CV disease. Based on one large trial (the hypertension optimal treatment trial; HOT trial), ASA taken for five years reduced MI (absolute risk reduction; ARR, 0.5%, number needed to treat; NNT 200 for 5 years), increased major haemorrhage (absolute risk increase; ARI, 0.7%, number needed to harm; NNH 154) and did not reduce all cause mortality or CV mortality. There was no significant difference between ASA and clopidogrel for the composite endpoint of stroke, MI or vascular death in one trial (clopidogrel versus aspirin in patients at risk of ischaemic events — CAPRIE, 1996). In two small trials warfarin alone or in combination with ASA did not reduce stroke or coronary events.

The Cochrane authors' conclusions were: 'For primary prevention in patients with elevated blood pressure, anti-platelet therapy with ASA cannot be recommended since the magnitude of benefit, a reduction in MI, is negated by a harm of similar magnitude, an increase in major haemorrhage. For secondary prevention in patients with elevated blood pressure (ATC meta-analysis: APTC 1994) antiplatelet therapy is recommended because the magnitude of the absolute benefit is many times greater. Warfarin therapy alone or in combination with aspirin in patients with elevated blood pressure cannot be recommended because of lack of demonstrated benefit. Glycoprotein IIb/IIIa inhibitors as well as ticlopidine and clopidogrel have not been sufficiently evaluated in patients with elevated blood pressure.'

Primary prevention

There have been six RCTs to evaluate the use of aspirin in primary prevention of CV disease in people without diabetes and the results of these have been combined in a sex-specific meta-analysis.[11] Three studies included only males, one included only females and two included both sexes.

Aspirin was associated with a statistically significant decrease in CV events in women (odds ratio and 95% confidence limits; OR 0.88, 95% CI: 0.79 to 0.99, P<0.03) and men (OR 0.86, 95% CI: 0.78 to 0.94, P=0.01) compared with placebo.

In women, aspirin was associated with a statistically significant reduction in the occurrence of stroke (OR 0.83, 95% CI: 0.70 to 0.97, P=0.02). When stroke sub-type was investigated, aspirin was associated with a reduction in ischaemic stroke but not haemorrhagic stroke. There was no statistically significant effect on MI, CV and all-cause mortality for women.

In men, aspirin was associated with a statistically significant reduction in the occurrence of MI (OR 0.68, 95% CI: 0.54 to 0.86, P<0.001), but had no statistically significant effect on stroke overall (although there was a statistically significant increase in haemorrhagic stroke) and no effect on CV and all-cause mortality.

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Aspirin therapy increased the risk of bleeding in both men and women. In absolute terms aspirin therapy for an average of 6.4 years resulted in an average absolute benefit of approximately 3 CV events prevented per 1000 women and 4 CV events prevented per 1000 men. Aspirin therapy for an average of 6.4 years resulted in an average absolute increase of approximately 2.5 major bleeding events caused per 1000 women and 3 major

Table 1. Benefits and major bleeding risk of aspirin therapy[12]

Women		
	RRR (CI)	**NNT (CI)**
Major CV composite	12% (1 to 21)	322 (184 to 3870)
Stroke	17% (3 to 30)	445 (252 to 2523)
	RRI (CI)	**NNH (CI)**
Major bleeding	67% (13 to 150)	323 (145 to 1684)
Men		
	RRR (CI)	**NNT (CI)**
Major CV composite	13% (6 to 21)	155 (98 to 363)
MI	32% (14 to 45)	116 (80 to 266)
	RRI (CI)	**NNH (CI)**
Major bleeding	71% (35 to 119)	292 (176 to 599)

Key: RRR = relative risk reduction; RRI = relative risk increase; NNT = number needed to treat; NNH = number needed to harm. Data are taken from Thompson, 2006.[12]

bleeding events caused per 1000 men. The benefits versus risk of major bleeding of aspirin therapy found in this study are expressed as RRRs and NNTs versus RRIs and NNHs in Table 1.[12]

Discussion

Aspirin is responsible for significant gastrointestinal morbidity. A local audit conducted in Derbyshire on patient emergency admissions for iron deficiency anaemia found that aspirin was implicated as a causative factor in several cases; 22% of patients admitted to hospital had aspirin classed as the major causative factor.

Because, by definition, primary prevention means that people do not have disease we should be even more demanding that there is strong evidence before recommending treatment. There does not appear to be sufficient evidence to support the use of aspirin in primary prevention. Locally, the area prescribing committee has agreed that there should be no new prescribing of aspirin for primary prevention. Existing patients should have the chance to discuss the lack of evidence for benefit and possibility of harm at their next review and be involved in a decision about whether to stop the aspirin. People who have existing symptomatic vascular disease should continue to be prescribed aspirin.

There is no evidence to support the use of clopidogrel in primary prevention because this has not been investigated in trials. Furthermore, clopidogrel is not licensed for primary prevention of CV events.

Declarations of interest

The author has no interests to declare.

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