Low-dose aspirin for cardiovascular protection in diabetes: Is it still justified?

Deborah Wake, John McKnight

Aspirin use in people with established cardiovascular disease (CVD) is well founded; however, its use in primary prevention, even in high-risk populations, has never been proven beneficial. Despite the lack of evidence, many guidelines advocate the use of low-dose aspirin in older people with diabetes. This article reviews the literature on this topic, including the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) study, published recently in the *British Medical Journal*. This prospective randomised trial addresses this issue in a UK-based population with diabetes and asymptomatic peripheral vascular disease. It provides further evidence that aspirin does not afford cardiovascular protection in the absence of proven symptomatic CVD.

Myocardial infarction (MI) and stroke are major causes of morbidity and mortality in type 1 and type 2 diabetes (Bell, 1994; Yudkin et al, 1996). Diabetes increases cardiovascular risk approximately two- to five-fold compared with that in the general population (Fuller et al, 1980; Rosengren et al, 1989; Bell, 1994; Yudkin et al, 1996). Indeed, one study from Finland noted that diabetes increases an individual's risk of a future cardiovascular event to the same as that of an age-matched person without diabetes who has already had a heart attack or stroke (Haffner et al, 1998). As a result, people with diabetes but no symptoms of cardiovascular disease (CVD) receive aggressive cardiovascular risk management with treatments normally reserved for those with pre-existing vascular disease.

Strategies for the primary prevention of CVD in diabetes have been widely extrapolated from secondary prevention guidelines, resulting in the liberal use of statins, antihypertensive drugs and aspirin. These changes have been quickly incorporated into local and national diabetes guidelines (Nicolucci et al, 2007).

The use of statins and antihypertensives in this population has been justified by the findings of large-scale clinical trials (UK Prospective Diabetes Study Group, 1998; Collins et al, 2003; Cheung, 2008; Cholesterol Treatment Trialists' Collaborators, 2008), but aspirin use remains questionable.

Article points

1. Many guidelines advocate the use of low-dose aspirin for primary prevention of CVD in diabetes.
2. However, this use of aspirin is controversial, with a number of studies showing predominantly negative results.
3. A recent prospective randomised trial (POPADAD) reinforces the view that low-dose aspirin for primary prevention of CVD in diabetes is no longer justified.
4. UK guidelines suggesting otherwise should be reviewed.

Key words

- Aspirin
- Diabetes
- Cardiovascular disease
- Primary prevention

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Page points

1. The POPADAD (2008) study evaluated whether aspirin and antioxidant therapy, either combined or alone, are more effective than placebo in reducing cardiovascular events in people with diabetes and asymptomatic peripheral arterial disease.
2. A total of 1670 people with type 1 or type 2 diabetes and asymptomatic peripheral vascular disease took part in the multicentre, randomised, double-blind, placebo-controlled trial.
3. Participants were recruited from 16 hospital diabetes centres and 188 primary care groups across Scotland.
4. Peripheral arterial disease increases the risk of subsequent CVD; the POPADAD authors used this high-risk group for the trial to increase the power of the study to answer the primary questions while enabling trial duration and number of participants to be reduced.

Antiplatelet agents and primary prevention of CVD

The use of antiplatelet drugs is known to reduce future cardiovascular events in populations both with and without diabetes with previous CVD (Sivenius, 1992; Antithrombotic Trialists' Collaboration, 2002). Their role in primary prevention, however, is more controversial, with a number of studies showing predominantly negative results.

The Physicians' Health Study published in 1989 randomised 22 071 healthy men to aspirin or placebo and found no benefit for the primary endpoint of cardiovascular mortality, although a subgroup analysis found that aspirin prevented non-fatal MI. The major cardiovascular event rates were less than 1% per year.

Meta-analysis of four randomised controlled trials in 2001 (Sanmuganathan et al) also demonstrated that aspirin decreased MI rates, but it did not reduce total mortality and may have increased the risk of stroke or major bleeding. The Antithrombotic Trialists' meta-analysis in 2002 subsequently concluded that there was no benefit from antiplatelet therapy for primary prevention.

In 2005, the Women's Health Study (Ridker et al) randomised 39 876 healthy women to treatment with either aspirin or placebo and also failed to show a significant improvement for the primary endpoint (prevention of non-fatal MI, non-fatal stroke, or death from cardiovascular causes; P=0.13). It did, however, appear to reduce the risk of stroke in women.

There have been few studies in a population consisting solely of people with diabetes. However, one study – the Primary Prevention Trial in 2003 (Sacco et al) – compared aspirin with placebo in people with type 2 diabetes who did not have established CVD. It failed to achieve a significant difference in the composite cardiovascular endpoint.

The POPADAD study

The POPADAD (Prevention of Progression of Arterial Disease and Diabetes) study published recently in the *British Medical Journal* (Belch et al, 2008) adds further weight to the theory that primary prevention with low-dose aspirin is not beneficial. POPADAD is a multicentre, randomised, double-blind, placebo-controlled trial. It evaluated the efficacy and safety of aspirin (100 mg daily) and antioxidant (alone or combined) compared with placebo in a 2x2 factorial design. The antioxidant contained α-tocopherol 200 mg, ascorbic acid 100 mg, pyridoxine hydrochloride 25 mg, zinc sulphate 10 mg, nicotinamide 10 mg, lecithin 9.4 mg, and sodium selenite 0.8 mg.

Defence against free radical attack may be lowered in people with diabetes (particularly those with peripheral vascular disease; Belch et al, 1989; Jennings et al, 1992), who may thus theoretically benefit from antioxidant treatment.

The POPADAD study population of 1670 people was recruited from 16 hospital diabetes centres and 188 primary care groups across Scotland. The participants had a history of type 1 or type 2 diabetes and were determined as having asymptomatic peripheral vascular disease as detected by a lower than normal ankle–brachial pressure index (ABPI) of <0.99.

Peripheral vascular disease has previously been shown to be a marker of systemic atheroma, even in the absence of symptoms. People with peripheral arterial disease have an increased risk of subsequent MI and stroke and are up to six times more likely to die from CVD within 10 years than patients without peripheral arterial disease (Criqui et al, 1992; Fowkes et al, 2008). By using this higher risk group, the authors would have expected a high event rate during the trial period, thus increasing the power of the study to answer the primary questions while enabling the trial duration and number of participants to be reduced.

POPADAD results

Participants had a mean age of 60 years with an average ABPI of 0.9. They were followed up for between 4.5 and 8.6 years (mean 6.7 years). The observed risk of a major cardiovascular event was high at 2.9% per year, equating to 233 participants experiencing one of the main outcome measures: death from coronary artery disease or stroke, non-fatal MI or stroke, or above-ankle amputation for critical limb ischaemia. Secondary endpoints in the trial

included all-cause mortality and other vascular events.

The headline result was that event rates were no different in those receiving aspirin than in those receiving placebo (116 events in the aspirin group versus 117 in the control group [See *Figure 1*]). While the authors of the study admit that it is possible that small effects could be missed owing to the size of the trial, they believe that they are highly unlikely to have missed anything of clinical importance.

Not surprisingly, dyspepsia was increased in the aspirin group (P=0.015), but no difference was seen between the groups in other adverse event rates in this study.

The use of antioxidants also did not appear to change vascular event rates, although concerningly all-cause mortality was slightly higher in those receiving treatment. The authors of the study believe that this was due to a sparsity of deaths in the no-antioxidant group (lower than predicted rates for this population) rather than an effect of the drug per se.

Discussion

The POPADAD study adds further weight to the argument that the use of aspirin for primary prevention of cardiovascular events in diabetes is unfounded. Moreover, we would add that inappropriate aspirin use may cause harm. Aspirin is associated with higher rates of bleeding, especially from the gastrointestinal tract. Although the individual risk is small, with large numbers of people taking aspirin the overall population risk is substantial.

There are many theories as to why aspirin does not provide benefit in this context. One possibility is that statin therapy is now so effective

Page points

1. The POPADAD study found no difference in event rates between the aspirin group and placebo group (116 vs. 117 respectively), reinforcing the argument that aspirin use for primary prevention of CVD in diabetes is unfounded.
2. Moreover, we would add that inappropriate aspirin use may cause harm.
3. Although the individual risk is small, with large numbers of people taking aspirin the overall population risk is substantial.

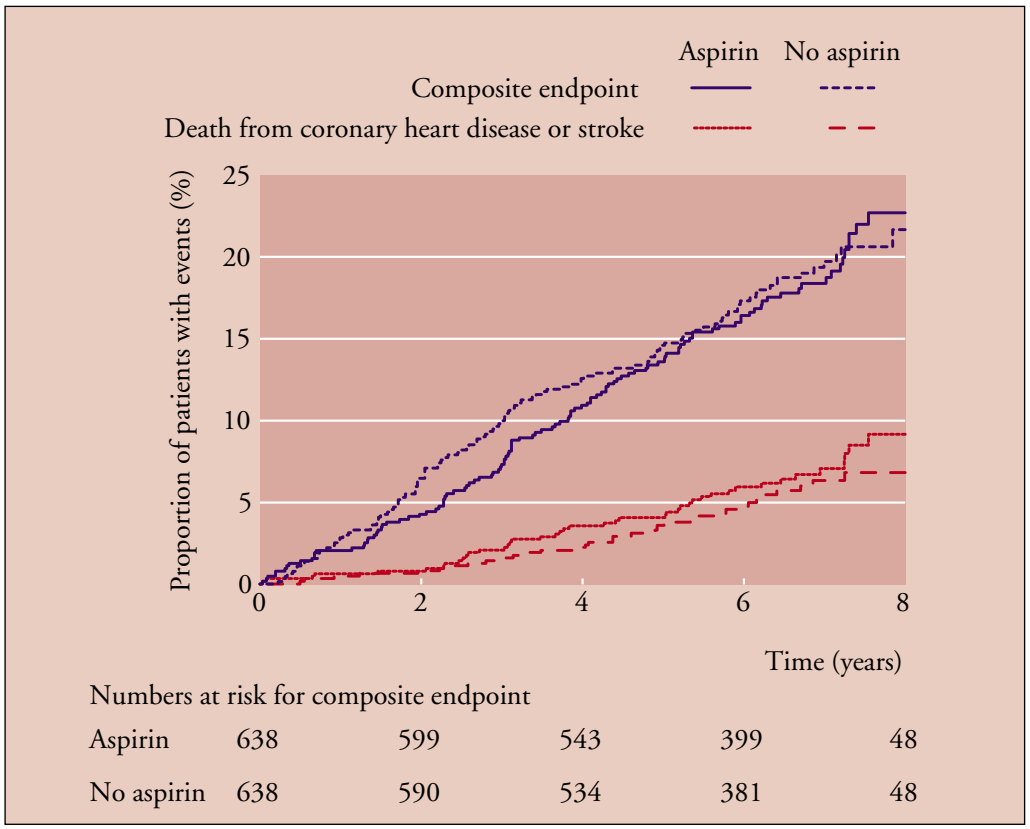

Figure 1. Kaplan–Meier estimates in aspirin and no aspirin groups of proportion of patients who experienced the composite endpoint of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or above-ankle amputation for critical limb ischaemia; and death from coronary heart disease or stroke. (Reproduced from BMJ, Belch et al 337: 1806–50, 2008, with permission from BMJ Publishing Group Ltd.)

Page points

1. Most studies have assessed the effect of low-dose aspirin only, and it cannot be assumed that other antiplatelet drugs or higher doses of aspirin are also ineffective.
2. Indeed, there is some evidence that other antiplatelet agents are beneficial in peripheral vascular disease.
3. Further studies are required before antiplatelet use in primary prevention can be completely dismissed.

at reducing risk that the additional benefit of aspirin is negligible. Perhaps in a pre-statin era, a different result would have been observed. Over the period of the POPADAD study, average cholesterol levels dropped from 6.0 mmol/L to 4.3 mmol/L, reflecting increased statin use.

In addition, we cannot assume that CVD and cerebrovascular disease in diabetes has the same pathophysiology as in the general population. We should not assume that secondary prevention treatments will automatically work for primary prevention in this high-risk group.

Most studies to date (including POPADAD) have assessed the effect of low-dose aspirin only and we cannot assume that either higher doses of aspirin or other antiplatelet drugs are also ineffective. Indeed, there is some evidence that other antiplatelet agents are beneficial in peripheral vascular disease (CAPRIE steering committee, 1996; Antithrombotic Trialists' Collaboration, 2002). Further studies are required before antiplatelet use in primary prevention can be completely dismissed.

Guidance

In 2003, the Food and Drug Administration (FDA) decided not to extend the labelling of aspirin for primary prevention. Some 6 years on, the UK is now coming to the same conclusion. As the evidence mounts, aspirin use for primary prevention of vascular disease in people with diabetes can no longer be justified. The many UK guidelines suggesting otherwise should be revised.

There is good and substantial evidence for the use of long-term aspirin following a vascular event in both the general population and those with diabetes. The Antithrombotic Trialists' Collaboration (2002) meta-analysis found that aspirin was beneficial in people with acute MI or ischaemic stroke, unstable or stable angina, and previous MI, stroke or cerebral ischaemia. We would strongly support its ongoing use in this context. There is no substantial evidence, however, for its use in people with purely peripheral vascular disease (Lechat and Priollet, 2006).

While guidelines are useful for population management, they require constant scrutiny and revision. An individualised approach is also required when considering primary prevention treatment in diabetes. Age, blood pressure, cholesterol level, family history, smoking and social status should be taken into consideration and risk calculators employed to help with decision making. Risk should be treated accordingly, with the use of antihypertensive agents and cholesterol-lowering drugs where appropriate. There is, however, no justification now for the use of low-dose aspirin for primary prevention of CVD. ■

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"While guidelines are useful for population management, they require constant scrutiny and revision. There is no justification now for the use of low-dose aspirin for primary prevention of CVD."

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This article, based on the POPADAD study (Belch et al, 2008), correctly casts doubt on the validity of giving aspirin to people with type 2 diabetes, who do not have proven cardiovascular disease. An article published more recently further reinforces this argument. In this study, Japanese investigators conducted a multicentre randomised, blinded, endpoint trial (Ogawa, 2008). They enrolled 2539 people with type 2 diabetes without a history of atherosclerotic disease and followed them up for 4.37 years. Participants were assigned to the low-dose aspirin group or the no aspirin group. Like the POPADAD study, in this study of people with type 2 diabetes, low-dose aspirin as primary prevention, did not reduce the risk of cardiovascular events.

NICE guidelines on the management of type 2 diabetes published in May 2008 recommend that people aged 50 years or over take low-dose aspirin (National Collaborating Centre for Chronic Conditions, 2008). While these recommendations are based on the concept that people with type 2 diabetes from mid-life onwards have a "cardiovascular disease equivalent", the evidence from both of these recent trials does not support this NICE guidance.

Primary care teams will be accustomed to managing individuals with diabetes on a case-by-case basis. The evidence of harm from gastrointestinal bleeding with aspirin is well documented, but now in people with diabetes there would appear to be less evidence for benefit in primary prevention, and primary care teams will be less pro-active in offering aspirin, or other antithrombolytic therapy as primary prevention. ■

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