Results of the ASCEND study: time to abandon aspirin for the primary prevention of cardiovascular disease in people with diabetes

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Cardiovascular disease remains the most common cause of premature mortality in people with diabetes.[1] While there is significant evidence for the use of statins for primary prevention of cardiovascular disease in people with diabetes, the benefit of other drugs, particularly aspirin, is much less certain.[2–4] There have been three large-scale primary prevention trials of aspirin in different patient populations published within the past year. ASCEND (A Study of Cardiovascular Events in Diabetes) examined the benefits of aspirin for the primary prevention of cardiovascular disease in people with diabetes.[5] In a 2 by 2 design, ASCEND also examined whether omega-3 fatty acid supplementation reduced cardiovascular risk in the same population.[6] The ASPREE trial was in healthy elderly subjects, and the ARRIVE trial was in subjects at moderate risk of cardiovascular disease. The results of the three studies were broadly similar.[7,8]

The ASCEND study

The ASCEND Study Group sought to establish the risk:benefit ratio of aspirin in people with diabetes. The study was designed and conducted by independent investigators at the Clinical Trial Service Unit at the University of Oxford. Potential participants were identified and recruited from regional diabetes registers around the UK. Patients with a coded diagnosis of diabetes (of any type) over the age of 40 were included. Participants had no history of previous cardiovascular disease or any condition which would limit aspirin administration. Patients who had another clear indication for aspirin therapy within current practice guidelines were excluded, as were potential participants who had comorbidity precluding the continued administration of aspirin. In all, 15 480 participants were identified for randomisation during the period from June 2005 to July 2011, with mean follow-up of 7.4 years.[5]

Participants were randomised to receive either 100mg aspirin or placebo. Follow-up questionnaires were sent to participants every six months which sought to ascertain compliance and whether the primary pre-specified efficacy outcome of first serious vascular event had occurred, defined as a composite of non-fatal myocardial infarction, non-fatal stroke (excluding intracerebral haemorrhage), TIA and death from any vascular cause excluding confirmed intracranial haemorrhage. The primary safety outcome was the occurrence of a serious haemorrhagic event, defined as intracranial haemorrhage, sight-threatening ophthalmic haemorrhage, gastrointestinal bleeding or any other serious bleeding (defined as any haemorrhage requiring hospitalisation, transfusion or a fatal bleed not included in the above categories). Responses from questionnaires were adjudicated by a medical panel.[5]

There was a significantly lower incidence of the primary adverse cardiovascular outcome in participants allocated aspirin compared to placebo. In total, 658 (8.5%) participants reported a primary efficacy outcome of serious cardiovascular event compared to 743 (9.6%) for the placebo group. This equated to a significantly reduced rate ratio of 0.88 (CI 0.79 to 0.97, p=0.01). The majority of the benefit was seen within the first five years with no further gain following this time. There was no difference in the rate of vascular deaths between the aspirin and placebo groups.[5]

The primary safety outcome of clinically important bleeding was significantly increased in the group receiving aspirin therapy. A total of 314 (4.1%) participants reported serious haemorrhage on aspirin therapy compared to 245 (3.2%) participants on placebo: a rate ratio of 1.29 (CI 1.09 to 1.52). The most common serious haemorrhagic complication was gastrointestinal bleeding, accounting for 41% of reported events. The next most common serious haemorrhagic event was sight-threatening ophthalmological haemorrhage accounting for 21% of the events, and 17% of events were intracranial haemorrhages. The remainder were haemorrhage not fitting into the above groups, including clinically significant haematuria. Fatal bleeding occurred in 0.2% of both arms of the study.[5]

A secondary end-point of this study was the risk of gastrointestinal tract cancer, and there was no significant difference in the incidence of cancer and cancer death between aspirin and placebo. However, the mean 7.4 year follow-up in the ASCEND may not be sufficient to reveal an association with reduced cancer in the medium to longer term.[5]

Overall, there was a 12% reduction in cardiovascular events in the aspirin group at the expense of a 29% higher risk of major bleeding events compared to placebo. The ASCEND authors concluded that the significant benefit from primary cardiovascular event reduction was outweighed by the increased risk of significant haemorrhagic events.[5]

ASCEND omega-3 fatty acids

The second component of the ASCEND study was to examine the primary preventative role of omega-3 fatty acids. Omega-3 fatty acids, sometimes called n-3 fatty acids, are polyunsaturated fatty acids. An association between increased omega fatty acid intake and cardiovascular risk reduction has been postulated from several observation studies.[9–11] Subsequent randomised

trials have demonstrated varying results on the merits of omega-3 supplementation and the postulated reduction in fatal and non-fatal cardiovascular events.[12,13] A recent meta-analysis of 10 studies failed to demonstrate any significant effect of omega-3 fatty acid administration as either a primary or secondary preventative agent.[14]

ASCEND randomised participants into receiving 1g capsules containing 840mg of n-3 marine fatty acids (as 460mg of eicosapentaenoic acid [EPA] and 380mg of docosahexaenoic acid [DHA]) or placebo (olive oil). The same primary outcome of first serious cardiovascular event was used as defined for the aspirin arm of the trial, and any reports of primary or secondary outcomes were adjudicated by clinicians blinded to the treatment arm.[6]

A serious vascular event occurred in 689 (8.9%) participants receiving n-3 fatty acid supplementation compared to 712 (9.2%) participants receiving placebo: a rate ratio of 0.97 with CI of 0.87 to 1.08 (p=0.55). The secondary outcome of a composite of serious vascular event or revascularisation occurred in 882 (11.4%) patients receiving treatment compared to 887 (11.5%) patients receiving placebo. All-cause mortality was reported in 752 (9.7%) participants within the treatment arm compared to 788 (10.2%) in the placebo group.[6]

The overall conclusion was that omega-3 fatty acid supplementation resulted in no significant difference in the incidence of serious adverse cardiovascular events in a diabetic population over a 7.4 year follow-up period.[6]

Who with diabetes should use aspirin?

The use of aspirin for secondary prevention following a serious vascular event is well established, and the relative risk reduction of further serious vascular events has been estimated to be up to 25%.[2,4,5] The risk reduction for vascular-related death is less.[5–8] Given the substantial benefit in reducing the risk of recurrent vascular events, the haemorrhagic risk from aspirin is outweighed in a secondary prevention population with diabetes.[5] The role of aspirin in primary prevention has been more contentious, largely due to the potential for serious adverse bleeding events which may outweigh any cardiovascular benefit in individuals who have not yet had a serious vascular event.[5,7,8]

A number of trials examining the role of aspirin as a primary prevention agent have been undertaken in recent decades to further elucidate whether aspirin is safe and effective in this setting.[5] Data from six trials published between 1988 and 2005 were examined in the Antithrombotic Trialists' Collaboration (ATC) meta-analysis from 2009; 95 000 participants of low average cardiovascular risk (<10% over 10 years) were included, which equated to 660 000 person years.[4] This meta-analysis found that aspirin as a primary preventative intervention yielded a 12% proportional reduction in serious vascular events. The predominant component of this reduction was in non-fatal myocardial infarction, and the effect on reduction of stroke or vascular death was not significant. The major side-effect of haemorrhage was predictably increased in participants allocated to aspirin therapy. Major gastrointestinal and extracranial bleeds were increased: 0.10% vs 0.07% per year.[4]

Within these trials, only 4% of participants had diabetes.[4,5] Within this subgroup, the relative cardiovascular benefits and risks appeared to be of the same magnitude as that of the general population.[4,5] Since the publication of the ATC meta-analysis in 2009, a further four trials examining primary prevention have been undertaken, and two of these studies were specifically in people with diabetes. POPADAD (Prevention of Progression of Arterial Disease and Diabetes) published in 2008 and another randomised control trial published in 2008 failed to demonstrate a definite benefit from aspirin in reducing cardiovascular risk.[15,16] While the ASCEND study has demonstrated modest reductions in non-fatal cardiovascular events, it is counterbalanced by an increase in haemorrhagic side effects.[5] There are similar findings reported for aspirin used for primary prevention in those with moderate vascular risk (ARRIVE), and healthy elderly subjects (ASPREE). In ASPREE, total mortality was increased.[7,8]

Summary

Aspirin is a readily available and cost-effective therapy in the secondary prevention of cardiovascular disease. While the role of aspirin as a primary preventative agent has previously been uncertain, the three large studies published in the last year have clarified the evidence for clinicians. Aspirin as a primary preventative agent although effective in reducing cardiovascular events is outweighed by the significantly increased risk of bleeding. Aspirin should not routinely be prescribed as a primary preventative agent in those with or without diabetes. Other methods of cardiovascular risk reduction, including optimal glycaemic control, blood pressure management, smoking cessation and lipid lowering therapy should be the priority for clinicians managing cardiovascular risk.

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Declaration of interests

There are no conflicts of interest declared.

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References are available in *Practical Diabetes* online at www.practicaldiabetes.com.

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