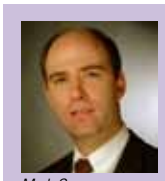
What role for aspirin and antioxidants in the prevention of cardiovascular events?

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the panel focus on the findings of a trial assessing the efficacy of aspirin and antioxidants in prevention of cardiovascular disease and death among people with diabetes.



Mark Savage, Consultant Physician in Diabetes and Endocrinology, Manchester, and Chair of North East Manchester Diabetes Network.

Those who wish to reduce the management of diabetes to the status of cook-book medicine are having a torrid time. The publication of the recent POPADAD study (Prevention of Progression to Arterial Disease and Diabetes; summarised alongside) has added to the ever-expanding debate over the ideal management of the "typical" patient.

In a 2×2 design, this Scottish group randomised 1276 people with either type 1 or type 2 diabetes, who were over 40 years of age and who had reduced ankle–brachial pressure (that is, less than 1), to placebo or aspirin 100 mg per day, as well as to antioxidant or placebo. The study failed to recruit the target number of 1600 participants, but, nevertheless, even overly optimistic scrutiny of the Kaplan-Meier plots of the aspirin versus the placebo groups confirm what the statistical tables tell; there was no benefit in the prevention of major cardiovascular events in those who were randomised to aspirin. Neither was there an excess in gastrointestinal bleeding events, although any individual with a hint of peptic ulcer disease or indigestion had been excluded. This finding confirms the meta-analysis published in 2002 (Antithrombotic Trialists' Collaboration, 2002).

No study is perfect, and this one also has its detractors and critics, as evidenced by the rapid responses to the article on the *British Medical Journal* website. However, the use of aspirin for primary prevention in high-risk individuals with diabetes is so unclear that its prescription should not be treated as unthinking dogma.

This study also throws the recommendation of NICE in its updated clinical guideline on type 2 diabetes (National Collaborating Centre for Chronic Conditions, 2008) into the frame, and raises the question of why aspirin use is recommended in high-risk people below 50 years of age, and in all those (if no contraindications) 50 or over, when the POPADAD study seems mainly to be confirming the evidence that already existed – that is, that aspirin is not of proven benefit for primary prevention in people with diabetes.

Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* **324**: 71–86

National Collaborating Centre for Chronic Conditions (2008) *Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (update)*. Royal College of Physicians, London

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The POPADAD study 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. Japanese investigators conducted a multicentre, randomised, blinded, endpoint trial (Ogawa et al, 2008; summarised on page 54). They enrolled 2539 people with type 2 diabetes without a history of atherosclerotic disease and followed them for 4.37 years. Participants were assigned to the low-dose aspirin group or the no aspirin group. As in the POPADAD study, in this trial, low-dose aspirin for 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 for this purpose.

National Collaborating Centre for Chronic Conditions (2008) *Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (update)*. Royal College of Physicians, London

Ogawa H, Nakayama M, Morimoto T et al (2008) Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* **300**: 2134–41

The prevention of progression of arterial disease and diabetes trial

Belch J, MacCuish, Campbell I et al (2008) *British Medical Journal* **337**: a1840

BMJ

Aspirin, antioxidants do not prevent cardiovascular disease or death among people with diabetes

1 The POPADAD (Prevention of Progression to Arterial Disease and Diabetes) trial sought to determine the effectiveness of aspirin and antioxidant therapy (combined and alone) versus placebo in reducing the development of cardiovascular events and asymptomatic peripheral arterial disease in people with diabetes.

2 These clinical criteria were selected by the authors, who cited a number of guidelines that, without evidential support, were recommending the use of aspirin in patients with diabetes and asymptomatic peripheral vascular disease for the prevention of cardiovascular disease.

3 It is known that aspirin is effective in the secondary prevention of cardiovascular events in participants with asymptomatic peripheral arterial disease, with or without diabetes.

4 This multicentre, randomised, double-blind, 2×2 factorial, placebo

controlled trial was conducted in 16 hospital centres in Scotland, with the support of 188 primary care groups.

5 Participants (n=1276) had type 1 or type 2 diabetes, were ≥40 years old and had an ankle–brachial pressure index of ≤0.99, which was considered indicative of asymptomatic peripheral arterial disease.

6 Participants were randomised to four treatment arms, receiving either an 100 mg aspirin tablet plus antioxidant capsule (n=320), an aspirin tablet plus placebo capsule (n=318), a placebo tablet plus antioxidant capsule (n=320), or a placebo tablet plus placebo capsule (n=318) daily.

7 Trial outcomes were two hierarchical, composite primary endpoints: death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischaemia; and death from coronary heart disease or stroke.

8 Death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or above ankle amputation for critical limb ischaemia was experienced by 233 participants. Overall, 78 participants died from coronary heart disease or stroke.

9 No statistically significant interaction between aspirin and antioxidant treatments was found for either endpoint (composite primary endpoint P=0.88; death from coronary heart disease or stroke P=0.95).

10 Given the lack of interaction between aspirin and antioxidant treatments, those randomised to receive aspirin were compared with those who received no aspirin (placebo tablet), and those randomised to receive antioxidant with those receiving no antioxidant (placebo capsule).

11 There was no statistically significant between-group difference for aspirin versus no aspirin, or antioxidant versus no antioxidant, for either of the primary endpoints.

12 The authors conclude by saying that these findings do not negate the use of aspirin for the secondary prevention of cardiovascular disease in people with diabetes, in those cases where there is an evidence base.

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John McKnight, Consultant Physician, Western General Hospital, Edinburgh.

Aspirin's role in the secondary prevention of cardiovascular disease is well established. In contrast, evidence for its use for primary prevention in people with diabetes has been less convincing. Despite this, both British and American guidelines recommend it for primary prevention in this high-risk group of patients, on the basis of theoretical benefits founded on the strength of the evidence for its use in secondary prevention. The POPADAD study aimed to determine whether aspirin was more effective than placebo in reducing new-onset cardiovascular events in people with either type 1 or type 2 diabetes and sub-clinical peripheral arterial disease. Its conclusion that there was no difference in outcome between the aspirin and placebo groups in either of its composite primary endpoints over a median follow-up of 6.7 years is persuasive.

A key strength of the study was the routine use of statins and antihypertensive therapies to reduce cardiovascular risk within the trial, and it is possible that aspirin's failure to influence outcome merely represents a lack of incremental effect on a background of otherwise potent risk reduction. Perhaps, however, we should be cautious in dismissing a role for aspirin in the small group of individuals who may be intolerant of such agents.

Of note, the study population was selected to be at high-risk for subsequent cardiovascular events: participants were aged over 40 years, and all had an ankle–brachial pressure index (ABPI) of 0.99 or less, representing subclinical peripheral vascular disease. A higher cut-off of ABPI than the usual value of 0.9 was selected to take account of the fact that people with diabetes with peripheral vascular disease can have ABPIs in the normal range due to calcification of blood vessels. This may, however, have resulted in the inclusion of participants who had normal peripheral circulation, and contributed to the lower than expected event rates in the study. It does, however, seem unlikely that this impacted greatly on the results observed.

POPADAD's conclusion that aspirin conferred no benefit in the setting of primary prevention in diabetes provides compelling evidence against its routine use in this context, and guidelines should be altered accordingly. It is, however, important to keep in mind that its benefits in secondary prevention remain undisputed.

On a broader note, POPADAD provides a salient reminder that caution is required when recommending the use of a medication in a setting in which it has not been tested.

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Diabetes guidelines (such as the updated NICE type 2 diabetes guideline [National Collaborating Centre for Chronic Conditions, 2008]) recommend the use of aspirin for the primary prevention of cardiovascular disease in people with diabetes. Why?

In my opinion it is because (a) there is good evidence that aspirin is beneficial for secondary prevention and (b) diabetes is considered a coronary risk equivalent. Given those two statements, it could be thought of as logical to use aspirin in primary prevention.

Previously, there has only been a relatively small amount of direct evidence regarding the use of aspirin for primary prevention in people with diabetes. However, it has shown no statistically significant benefit of aspirin.

The well-designed and executed POPADAD trial, carried out on 1276 adults in Scotland, has again provided no evidence to support the use of aspirin for primary prevention in people with diabetes. Aspirin, even in the sort of small doses used in this trial, can cause harm. The number needed to treat to cause an adverse event that is quoted in the paper is 248. The adverse events include gastrointestinal bleeding, which increases with age and also continuous exposure. Although the calculated risk of major bleeding is small, the number of people taking aspirin is large and, therefore, in population terms, aspirin-induced gastrointestinal bleeding is a major problem.

It is interesting that a just-published systematic review and meta-analysis examining 13 papers reporting on coronary risk equivalence concludes that the data do not support the hypothesis that diabetes is a coronary heart disease equivalent (Bulugahapitiya et al, 2009).

I have always been skeptical about the benefits of aspirin in primary prevention. The tide of evidence now supports this skeptical view. I wonder when guidelines will be changed?

Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I (2009) Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet Med* **26**: 142–8

National Collaborating Centre for Chronic Conditions (2008) *Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (update)*. Royal College of Physicians, London