

RAPID APPRAISAL

Name of Trial: The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease

Reference: Belch J, MacCuish A, Campbell I et al. BMJ 2008; 337;a1840. doi:10.1136/bmj.a1840

Question: Does aspirin and antioxidant therapy, combined or alone, reduce the development of cardiovascular events in patients with diabetes mellitus and asymptomatic peripheral arterial disease?

Summary: In the POPADAD trial, neither aspirin, nor antioxidants, in combination or alone, were shown to be effective for primary prevention of cardiovascular events in patients with asymptomatic peripheral arterial disease and diabetes. As this study was underpowered, due to recruiting less than the required number of patients and a lower than predicted event rate, the results should be interpreted with caution. Current national guidance recommends aspirin 75mg daily for primary prevention in patients with diabetes who fulfil defined criteria, and until more robust evidence of lack of benefit is available, this practice should continue.

Did the study ask a clearly focussed question?

Yes - The study objective was to determine whether aspirin and antioxidant therapy, alone or in combination, were more effective than placebo in reducing the development of cardiovascular (CV) events in patients with type 1 or 2 diabetes mellitus and asymptomatic peripheral artery disease.¹ The median length of follow up was 6.7 years.¹

There were two composite primary end points: (1) death from coronary heart disease (CHD) or stroke, non-fatal myocardial infarction (MI) or stroke, or above ankle amputation for critical limb ischaemia; and (2) death from CHD or stroke.¹

Secondary end points included all cause mortality, non-fatal MI, and occurrence of other vascular events, including stroke, transient ischaemic attack, coronary or peripheral arterial bypass surgery, coronary or peripheral arterial angioplasty, development of angina, claudication, or critical limb ischaemia.¹

Was the study design appropriate?

Yes - This study, carried out in Scotland, was a prospective multi-centre, randomised, double-blind, 2x2 factorial placebo controlled trial. Inclusion criteria were adults of either sex, aged ≥ 40 years, with type 1 or 2 diabetes, and had asymptomatic peripheral arterial disease as detected by a lower than normal ankle brachial pressure index (≤ 0.99).¹

The use of antiplatelet agents is known to reduce future secondary CV events in patients with both diabetes and CV disease and in patients with peripheral arterial disease.² There are few data on aspirin for primary prevention in patients with diabetes.^{3,4}

As studies of patients with diabetes and peripheral artery disease have linked platelet aggregation with

oxidative stress, with free radicals increasing, and antioxidants decreasing, platelet aggregation, the investigators included an antioxidant capsule as part of the study.¹

Were participants appropriately allocated to intervention and control groups?

Yes - Potentially eligible participants attending the diabetes clinics during the enrolment period were invited to join the trial. After providing written consent, participants were randomised to aspirin plus antioxidant capsule (n = 320), aspirin plus placebo (n = 318), placebo plus antioxidant (n = 320) or placebo plus placebo (n = 318). The allocation sequence was randomised and computer generated.¹ The dose of aspirin used was 100mg once daily;¹ this strength of tablet is not available in clinical practice.

Were participants, staff and study personnel 'blind' to participants study group?

Yes - Participants and staff involved in providing care were blinded to group assignment, and all primary and secondary end points were adjudicated on a blinded basis by a committee. The placebo tablets and capsules were identical in appearance to the active tablets and capsules, and an independent pharmacist packaged the drugs to ensure allocation concealment.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes - Of the 1276 adults who started the trial, 1074 participants had their final follow up in 2006; six had moved away and were lost to follow up, one withdrew consent and 195 died during the trial. A consort flowchart accounted for all randomised patients up to entry into intention to treat analysis.¹

Were the participants in all groups followed up and data collected in the same way?

Yes – Follow-up evaluations were done every six months, when outcome measures, adverse events and interventions were recorded. Electrocardiography results were recorded at the baseline visit and annually thereafter. ECGs were reviewed manually for evidence of silent MI.¹

Was the study large enough?

No – The study was originally designed to recruit 1600 participants and follow up each for four years. An estimated 392 events occurring during the trial would have provided 90% power to detect a 25% relative reduction in primary outcomes at the 5% level of significance.¹

The estimated numbers were however not recruited and the event rate was lower than predicted. A retrospective power calculation using the 1276 participants recruited, suggested that 256 events occurring during the trial would provide 73% power to detect a 25% relative reduction in event rate, a lower level of power than would normally be accepted for a clinical study.¹

At the end of the study only 233 events had occurred after a median follow up 6.7 years.¹ This was lower than the original, and retrospective power calculations, and suggests the study was underpowered to answer the question posed.

How are the results presented, and what is the main result?

The composite primary end point* was experienced by 233 patients, and 78 died from CHD or stroke.¹

	Composite end point *	CHD or stroke
Aspirin plus antioxidant (n = 320)	n = 58 (18%)	n = 23 (7%)
Aspirin plus placebo (n = 318)	n = 58 (18%)	n = 20 (6%)
Placebo plus antioxidant (n = 320)	n = 59 (18%)	n = 19 (6%)
Placebo plus placebo (n = 318)	n = 57 (18%)	n = 16 (5%)
P value (Test for interaction between aspirin and antioxidant)	0.92	0.90

* Death from coronary heart disease or stroke, non fatal myocardial infarction or stroke, or above ankle amputation for critical limb ischaemia

There was no significant difference between patients who were randomised to aspirin vs. no aspirin ($p = 0.86$ and $p = 0.36$), or those randomised to antioxidant vs. no antioxidant ($p = 0.85$ and $p = 0.40$), for the composite primary end point*, or death from CHD or stroke, respectively.¹

Neither aspirin, nor antioxidants were demonstrated to be effective for the primary prevention of CV events in patients with asymptomatic peripheral arterial disease and diabetes in the population studied.¹

There was a statistically significant ($p = 0.006$) increase in the number of deaths from any cause in the antioxidant group.¹

The incidence of gastrointestinal symptoms and gastrointestinal bleeding were not increased in patients taking aspirin compared to those not taking aspirin; 11.4% vs 14.7% ($p = 0.081$), and 4.4% vs 4.9% ($p = 0.69$), respectively.¹

How precise are the results?

The interaction between aspirin and antioxidant treatments was not statistically significant for the composite primary end point ($p = 0.92$) or death from CHD or stroke ($p = 0.90$). Because there was no evidence of interaction between aspirin and antioxidant, patients in the two groups randomised to receive aspirin were compared with those in the two groups randomised to receive placebo tablets (no aspirin), and those in the two groups randomised to receive antioxidant were compared with those in the two groups randomised to receive placebo capsules (no antioxidant).¹

The 95% confidence limits (CI) were wide, with the lower limit only just excluding a 25% benefit for aspirin and 23% benefit for antioxidants. At the upper limit, the CI only just excluded 27% and 34% increases in CV events, respectively.¹

Can the results be applied to the local population?

Yes – The results can be applied cautiously to the local population, taking into account the similar results of previously published studies and the inadequate statistical power. The study was carried out in Scotland, and therefore demographics were likely to be similar to our local population.

The participants had mean ages of 60-61 years, about 56% of them were women, time since diagnosis of diabetes ranged from 2.4 to 13.0 years, and about 32% were treated with insulin. Mean HbA_{1c} was 7.9 - 8.0%, mean total cholesterol was 5.5 – 5.6 mmol/l and the mean ankle brachial index was 0.89 – 0.91. Other patient characteristics such as smoking status, body mass index, blood pressure, and lipid profile were also reported, and generally representative of those seen in local practice.¹

The proportion of patients with type 1 vs. type 2 diabetes was not reported.

Participants received appropriate background CV risk reduction therapy as appropriate (e.g. statins) at the discretion of the investigators and clinicians.¹ Since the inception of the study, there is now a trend for use of higher dose statins. Two of the centres calculated that in > 10,000 people with diabetes, the mean total cholesterol level fell from of 6.0 mmol/l in 1996 to 4.3 mmol/l in 2007.¹

How does this study relate to current guidelines and evidence?

The guidelines and evidence regarding the use of antiplatelet therapy in asymptomatic patients with diabetes are contradictory and unclear.

Previous evidence from the Antithrombotic Trialist's meta-analysis, did not demonstrate benefit of antiplatelet therapy for primary prevention in patients with diabetes. The PPP study was discontinued early due to benefit accruing in non-diabetic patients receiving aspirin and so may have been underpowered to demonstrate a benefit in diabetic patients.^{2,5}

The HOT study did demonstrate a significant reduction in CV events in controlled hypertensive patients treated with aspirin but this benefit was wholly offset by an increase in the number of serious non-fatal bleeding events, although fatal bleeding events were not increased. Patients with diabetes mellitus gained similar benefits in CHD risk reduction as the rest of the HOT population.⁶

A Cochrane review (published in 2004, and re-published in 2008) based largely, on the evidence of the HOT study, concluded that aspirin should not be recommended for primary prevention of cardiovascular events in patients with hypertension as the benefit is negated by the harm.⁷

Nevertheless, the British Hypertension Society (BHS) recommends aspirin 75 mg daily for patients for primary prevention if the patient is aged ≥ 50 years with blood pressure controlled to $< 150/90$ mm Hg where there is target organ damage, diabetes, or a 10-year risk of CV disease of $\geq 20\%$.⁸

NICE guidance on the management of type 2 diabetes advises that aspirin 75 mg daily should be offered to people aged ≥ 50 years with adequately controlled blood pressure ($<145/90$ mmHg), or aged < 50 years with significant CV risk factors (metabolic syndrome, strong early family history of CV disease, smoking, hypertension, existing CV disease, microalbuminuria). The Guideline Development Group (GDG) acknowledged the paucity of direct evidence in patients with type 2 diabetes, and that their recommendations for treating people ≥ 50 years with aspirin 75 mg daily were somewhat arbitrary.⁴

Does aspirin and antioxidant therapy, combined or alone, reduce the development of cardiovascular events in patients with diabetes mellitus and asymptomatic peripheral arterial disease?

No – This trial did not demonstrate any benefit from either aspirin or antioxidant treatment on the primary end points of CV events and CV mortality in patients with asymptomatic peripheral arterial disease and diabetes.¹ The results should however be considered with caution due to the low statistical power of the study.

Aspirin has only been shown to be beneficial in patients with established symptomatic CV disease.^{6,8}

In asymptomatic diabetic patients the evidence of benefit is weak and contradictory, but the current consensus of expert opinion in national guidance is that diabetic patients who fulfil defined criteria, including, significant CV risk, should be offered treatment with aspirin.

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