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Aspirin therapy and primary prevention of cardiovascular disease in diabetes mellitus

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The benefits of aspirin therapy in reducing the subsequent risk of myocardial infarction, stroke and death is well documented in individuals with cardiovascular disease including those with diabetes mellitus (DM). The evidence for aspirin use in primary prevention of cardiovascular events in DM is debatable and meta-analyses do not suggest a proven benefit. Despite the lack of evidence, low-dose aspirin therapy has been recommended by many current diabetes guidelines. This article reviews the results of two recently published large randomized clinical trials that have looked at primary prevention of cardiovascular events using aspirin in patients with DM.

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Diabetes mellitus (DM) affects 2.5 million people in the UK and cardiovascular disease is a major cause of morbidity and mortality in these individuals [1]. There is a two- to fourfold increase in risk of death in patients with DM compared with those without [2]. A number of aggressive interventions are used in the treatment and prevention of cardiovascular disease in DM [3]. A part of such treatment is the use of antiplatelet medication, namely aspirin (acetylsalicylic acid). Patients with DM have alteration in platelet function including enhanced aggregation, greater expression of collagen surface receptors, increased markers of platelet activation and augmented thrombaxane synthesis [4,5]. Thus, antiplatelet agents in DM may be of particular benefit.

The use of aspirin in those with established cardiovascular disease has been shown to protect against further vascular events (secondary prevention) [6]. Two large meta-analyses of prospective trials of antiplatelet therapy after myocardial infarction, stroke or transient ischaemic attack or a history of cardiovascular disease were reported by the Anti-Platelet Trialists' Collaboration [6,7]. A 25% reduction in the vascular event rate was found in these high-risk patients, those with DM having similar comparable risk reductions [7].

In contrast, in primary prevention studies, a meta-analysis by the Anti-Platelet Trialists' Collaboration reported a non-significant 7% reduction in cardiovascular events in those with DM [6]. Many of the reported studies were subgroup analyses of larger clinical trials and therefore contained small patient numbers and lacked statistical power. Thus, the benefit of using aspirin in DM for primary prevention of cardiovascular events remains unclear.

Despite the lack of evidence, many current guidelines in Europe and the USA recommend the use of aspirin in patients with type 2 diabetes for the primary prevention of cardiovascular disease [8,9]. The American Diabetes Association 2009 guidelines recommend aspirin use in

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patients with diabetes above the age of 40 years or in those with additional cardiovascular risk factors. These guidelines acknowledge that these recommendations are based on conflicting and limited evidence [9].

The recent UK NICE 2008 guidelines on the management of type 2 DM advocate the use of low-dose aspirin for those 50 years or older and with a blood pressure below 145/90 mmHg or in younger individuals with additional cardiovascular risk factors such as hypertension, smoking, microalbuminuria or an early family history of cardiovascular disease [10].

The results of two recently published clinical trials have attempted to clarify the use of low-dose aspirin in patients with DM who had either asymptomatic peripheral vascular disease or had no cardiovascular disease [11,12]. These trials will be discussed in more detail and reviewed as to how they may affect current clinical management.

Prevention of Progression of Arterial Disease and Diabetes

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) study examined the use of 100 mg of aspirin or placebo in 1276 adults with DM aged 40 years or more and had asymptomatic peripheral vascular disease (table 1) [11]. Peripheral arterial disease was defined by an ankle-brachial index of $\leq$0.99. The double-blinded multicentre study had recruited patients from 16 centres in Scotland between 1997 and 2001. The primary endpoint was a composite of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke or above ankle amputation for critical ischaemia. No differences were found between the aspirin and non-aspirin groups for the primary endpoint [hazard ratio (HR): 0.98, 95% CI: 0.76–1.26, p = 0.86). Individual secondary endpoints were also not significant. The study had failed to achieve the target recruitment of 1600 patients and the event rate in the study was lower than had been predicted, reducing the overall power of the study. There was no significant increased risk of gastrointestinal bleeding between the two groups (4.4% aspirin vs. 4.9% no aspirin group).

Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes

The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial was designed to investigate whether low-dose aspirin therapy would be

Table 1 A comparison of the POPADAD and JPAD trials with the ATC meta-analysis for the usage of aspirin for primary prevention of cardiovascular events in patients with diabetes

	POPADAD	JPAD	ATC
Number (aspirin vs. no aspirin)	638 vs. 638	1262 vs. 1277	2568 vs. 2568
Mean age (years)	60–61	65	—
Mean diabetes duration (years)	5.7–6.7	7.3	—
Median duration of follow up (years)	6.7	4.37	—
Study design	Muliticentre double-blinded placebo	Muliticentre open-labelled blinded	Meta-analysis of nine randomized trials in diabetes participants
Primary endpoint (s)	Death from CHD or stroke, non-fatal MI or stroke or above ankle amputation; death from CHD or stroke	Composite of sudden death, or non-fatal MI,/angina, stroke/TIA or peripheral arterial disease	Serious vascular events (non-fatal MI or non-fatal stroke or vascular death)
Incidence of primary endpoint events	2.9 per 100 patient-years; 1.0 per 100 patient-years	1.36 per 100 patient-years	—
Aspirin dose used	100 mg	81–100 mg	75–650 mg
Study completion rate	14% at year 1; 50% at year 5	90% at study end	—
Hazard ratio (aspirin vs. no aspirin)	0.98 (95% CI: 0.76–1.26), p = 0.86; 1.23 (95% CI: 0.79–1.93), p = 0.36	0.80 (95% CI: 0.58-1.10), p = 0.16	7% risk reduction (odds ratio), p = ns
Gastrointestinal bleed (aspirin vs. no aspirin)	28 (4.4%) vs. 31 (4.9%), p = 0.69	12 (0.95%) vs. 4 (0.31%)*	—

ATC, Antithrombotic Trialists Collaboration; CHD, coronary heart disease; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI, myocardial infarction; POPADAD, Prevention of Progression of Arterial Disease and Diabetes; TIA, transient ischaemic attack.
*Significance between groups not determined.

beneficial for primary prevention of cardiovascular events in patients with type 2 DM (table 1) [12]. This was a multicentre randomized open-labelled trial conducted between 2002 and 2008 in Japan. The study had enrolled 2339 patients with type 2 DM without a history of cardiovascular disease and had a median follow up of 4.4 years. The two groups were randomized to either low-dose aspirin at a dose of 81–100 mg or to no aspirin. The primary endpoint was a composite of atherosclerotic events that included fatal or non-fatal ischaemic heart disease, fatal or non-fatal stroke and peripheral vascular disease.

No differences were found in the primary endpoint in the aspirin compared with the non-aspirin group (HR: 0.80, 95% CI: 0.58–1.10, $p = 0.16$). There were however some inconsistencies, the combined endpoint of fatal coronary and cerebrovascular events occurred in one patient in the aspirin group compared with 10 patients in non-aspirin group (HR: 0.10, 95% CI: 0.01–0.79, $p = 0.0037$), though confidence intervals were wide. The authors concluded that in type 2 DM, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events. No significant differences between the two study arms were found for the composite of gastrointestinal bleeding or haemorrhagic stroke [12].

Commentary

Many current guidelines recommend the use of low-dose aspirin in diabetes to prevent cardiovascular disease events such as myocardial infarction or stroke [8,10,13,14]. The hypothesis being that using aspirin is of proven benefit for the prevention of subsequent cardiovascular events (secondary prevention) in those who have already had a myocardial infarct or ischaemic stroke and therefore could be of benefit if taken by those at high risk, such as individuals with diabetes. The POPADAD and JPAD studies both found a lack of benefit of aspirin in the prevention of cardiovascular events in patients with type 2 diabetes who had asymptomatic peripheral vascular disease or no cardiovascular disease (primary prevention).

The cardiovascular event rate in the JPAD trial was predicted at 5.2 events per 100 patient-years; however, the actual rate was only 1.7 events per 100 patient-years [12]. The JPAD trial was therefore grossly underpowered and lacked precision and statistical power. The low baseline risk of cardiovascular events in this Japanese population questions whether this can be generalized to other populations in the western world with a substantially higher cardiovascular risk.

In the POPADAD trial, a higher risk population were recruited as these patients had an abnormal ankle–brachial index and therefore had asymptomatic peripheral vascular disease. It could be argued that the trial had recruited a high-risk diabetes patient population that had prior atherosclerotic disease and therefore was really a secondary prevention study with a particularly high risk for cardiovascular events. The annual cardiovascular event rate observed was 2%, while the authors stated that the event rate predicted at the commencement of the trial was 8–12% per annum [11]. In addition, the study had failed to recruit the target 1600 patients and therefore was significantly underpowered. The effect of aspirin use was reported as non-significant (HR: 0.98, 95% CI: 0.76–1.26, $p = 0.87$) in the POPADAD trial (table 1). The wide confidence intervals in this study however could suggest either a 24% relative reduction in cardiovascular events or a 26% relative increase in event rate.

The lower than predicted cardiovascular event rates in both these trials may have been because of the increasingly widespread use of statin therapy and other cardioprotective drugs compared with the period before the trial, thus reducing the frequency of primary events and hence overall power of study. Adherence to trial medication in the POPADAD was 50% at 5 years and therefore this could possibly account for the lack of benefit. It could also be speculated that the duration of therapy for the benefit of aspirin could take longer than the median follow up of 4–7 years, although there appeared to be no divergence of events observed in the two groups.

The POPADAD trial reported a similar frequency of gastrointestinal bleeding in the aspirin compared with the non-aspirin group at around 5% at 6.7-year follow up (table 1). In contrast, the JPAD reported the occurrence of gastrointestinal bleeding in the aspirin group at 0.95% at 4.37 years and was three times greater compared with the non-aspirin group, this is consistent with incidence data from large systematic reviews [15]. These discrepancies may have been the result of both trials being underpowered and therefore detecting small differences in rare events such as gastrointestinal bleeding would be unreliable or may have been because of differences in the reporting of symptoms.

Aspirin resistance has been speculated to be one reason for less effectiveness in those with DM [16]. It has been suggested that because of the increase in platelet turnover and thromboxane synthesis in DM, higher doses of aspirin may be needed [17]. Some authors have suggested that aspirin resistance is caused by non-compliance.[16] Use of high doses of aspirin in DM has been little studied and in the few clinical trials that used higher doses of aspirin (>300 mg daily), there appeared to be no additional

clinical benefit [18]. Furthermore, analyses from the Anti-Platelet Trialists' Collaboration concluded that low-dose aspirin was just as effective as higher doses [6].

The current evidence from the POPADAD and JPAD trials together with previous trial data do not support the universal widespread use of aspirin in primary prevention of cardiovascular events in diabetes. However, because these studies were inconclusive, further large adequately powered trials are necessary to definitively answer the question whether the routine use of aspirin for primary prevention of cardiovascular events is safe and effective in diabetes. The use of aspirin in primary prevention in diabetes should be based on an individual's cardiovascular risk and those with the highest risk offered treatment if this outweighs the risk.

Current guidelines based on consensus of expert opinion need to be reviewed and the decision to use aspirin needs to be made on an individual patient basis after careful evaluation of the balance of the expected benefits vs. the risk of gastrointestinal bleeding and haemorrhagic stroke. The outcome from larger ongoing aspirin trials in diabetes may provide clarification for the use of low-dose aspirin in the primary prevention of cardiovascular disease. The ASCEND (A Study of Cardiovascular Events iN Diabetes) study currently underway by the Oxford trials unit have calculated a sample size of 10 000 patients to detect whether low-dose aspirin has a benefit for primary prevention in diabetes [19]. The result of this and other studies in due course may provide clearer answers.

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