Diabetes journals

Aspirin for primary prevention of CVD: The controversy remains in diabetes

Marc Evans
Consultant Physician, Llandough Hospital, Cardiff

The role of aspirin for the primary prevention of cardiovascular disease (CVD) in people with diabetes remains a contentious issue. The current consensus is that aspirin should only be offered as primary prevention in people with an elevated risk (>10%) of CVD (Handelsman et al, 2011). Numerous meta-analyses have been conducted to evaluate the safety and efficacy of aspirin for CVD prevention in people with diabetes (Calvin et al, 2009; De Berardis et al, 2009; Younis et al, 2010; Zhang et al, 2010; Butalia et al, 2011). These analyses found no increase in the risk of bleeding with aspirin doses ranging from 100 mg every other day to 650 mg per day. However, no benefit in terms of preventing CVD endpoints, including all-cause mortality, CVD mortality, myocardial infarction and stroke, was identified either.

It would thus appear that aspirin has no benefit in terms of primary CVD prevention; however, these meta-analyses did not include other atherosclerotic endpoints, such as angina, transient ischaemic attack (TIA), peripheral artery disease (PAD) or revascularisation. Consequently, the meta-analysis by Kokoska and colleagues (summarised alongside) sought to evaluate aspirin's safety and efficacy in the primary prevention of CVD, including a full array of atherosclerotic events, in people with diabetes.

Following an extensive literature search, six studies with a total of 10 117 participants were identified as being pertinent to the issues under investigation, with median follow-up ranging from 3.6 to 10.1 years. There was no difference between aspirin and placebo with respect to the risk of all-cause mortality (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.81–1.06) or individual atherosclerotic events. In addition, there was no significant difference in the rates of bleeding (OR, 2.53; 95% CI, 0.77–8.34), gastrointestinal bleeding (OR, 2.14; 95% CI, 0.63–7.33) or haemorrhagic stroke rates (OR, 0.90; 95% CI, 0.34–2.33) between the treatments.

There are some limitations worth noting in this analysis. Firstly, a wide range of aspirin doses was evaluated in the studies, ranging from 100 mg to 625 mg daily. Secondly, not all of the trials assessed or reported all the efficacy and safety endpoints; that is, TIA, PAD and angina were only included in half of the trials, and the safety endpoints of bleeding, gastrointestinal bleeding and intracranial haemorrhage were only included in three trials each. As the number of participants for these endpoints is smaller than for the CVD endpoints, it is difficult to draw conclusions in terms of risk–benefit analysis from such data. A final confounding issue with respect to the safety profile of aspirin is the fact that the intervals between routine assessments in the studies varied from 2 weeks to 2 years, which may have led to under-reporting of adverse events in some studies.

Nevertheless, this meta-analysis helps provide further insight into the role of aspirin in CVD risk management in people with diabetes. The data suggest that aspirin may not be beneficial for the prevention of angina, TIA, PAD or revascularisation, while no evidence of harm due to excess bleeding could be identified.

It remains unclear whether aspirin may be beneficial for primary CVD prevention in certain subsets of people with diabetes; however, the results of studies such as ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes; De Berardis et al, 2007) and ASCEND (A Study of Cardiovascular Events iN Diabetes; ClinicalTrials.gov identifier: NCT00135226) may finally provide definitive answers to this question. ■

References on next page

Diabetes Res Clin Pract

Aspirin: No effect on atherosclerotic events in primary prevention

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 The objective of this meta-analysis was to evaluate the efficacy and safety of aspirin for primary prevention of cardiovascular disease (CVD) in people with diabetes, with a particular focus on atherosclerotic events, including angina, transient ischaemic attack (TIA), peripheral artery disease (PAD) and revascularisation.

2 Six randomised controlled trials, including 10 117 participants in total, were included in the analysis.

3 There was no significant difference in all-cause mortality, CVD mortality, myocardial infarction or stroke between aspirin and placebo.

4 There was no difference between groups in the rates of angina, TIA, PAD or revascularisation; however, the pool of participants for these endpoints was smaller than that for mortality and major adverse cardiac events.

5 There were no significant differences in the rates of bleeding, gastrointestinal bleeding or haemorrhagic stroke between groups.

6 Heterogeneity between the studies was high for nearly all endpoints, there was variation in baseline CVD risk between the studies and the time to follow-up among participants was highly variable.

7 Despite these limitations, the authors conclude that aspirin is not beneficial for the primary prevention of atherosclerotic events in people with diabetes. It remains unclear whether certain subsets of people with diabetes may benefit; however, future trials may elucidate this.

Kokoska LA, Wilhelm SM, Garwood CL, Berlie HD (2016) Aspirin for primary prevention of cardiovascular disease in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* **120**: 31–9

Diabetes Res Clin Pract

Effects of statin therapy on glycaemic control

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Statin therapy has been associated with both an increased incidence of T2D and a small but significant deterioration in glycaemic control in people who have the condition.

2 The aim of this retrospective study was to quantify the effects of statins on glycaemic control in a real-world cohort of people with T2D.

3 In total, 421 people attending their first T2D outpatient clinic, with an HbA_{1c} <64 mmol/mol (8.0%), were enrolled. Of these, 359 received a statin and 62 did not.

4 At 12 months' follow-up, statin recipients had not improved their mean glycaemic control in terms of either fasting plasma glucose (FPG) or HbA_{1c}. In contrast, those who did not receive statins had small reductions in FPG and HbA_{1c} of 0.4 mmol/L and 4.2 mmol/mol (0.4%), respectively.

5 Statin users were more likely to have a ≥5% increase in HbA_{1c} levels (31.7% vs 23.0%) and were less likely to meet HbA_{1c} treatment targets (62.0% vs 75.4%).

6 Statin users were also more likely to undergo intensification of antidiabetes therapy (48.7% vs 27.4%).

7 Subanalysis showed that high-potency statins had a greater effect on glycaemic control and treatment intensification than low-potency statins.

8 The authors conclude that, despite these effects, statins are still indicated to reduce cholesterol; however, physicians should be aware that intensification of diabetes therapy may be required.

Bardini G, Giannini S, Rotella CM et al (2016) Lower and higher-potency statins on glycemic control in type 2 diabetes: a retrospective cohort study. *Diabetes Res Clin Pract* **120**: 104–10

Diabetes Care

Does GDM raise CVD risk independently of T2D development?

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 Gestational diabetes (GDM) is associated with an increased risk of both T2D and cardiovascular disease (CVD) in later life.

2 This population-based cohort study was conducted to determine whether the increased risk of CVD could be explained purely by the development of T2D.

3 Data on 1 515 079 women who had a live birth between 1994 and 2014 were analysed. Of these, 41 299 had GDM but did not develop T2D over the median follow-up of 10 years, and 15 585 had GDM and went on to develop T2D.

4 Compared with women who developed neither condition, those who had GDM but did not develop T2D had no increase in risk of retinopathy, neuropathy or foot ulceration, while those who did develop T2D were, unsurprisingly, at increased risk.

5 However, women with GDM who did not develop T2D were found to have an increased risk of both CVD (hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.07–1.59) and coronary artery disease (HR, 1.41; 95% CI, 1.11–1.80).

6 The absolute event rates of the individual CVD outcomes were low, all at ≤1 per 1000 person-years.

7 Despite this limitation, the authors conclude that women with GDM are at increased risk of developing CVD, even in the absence of T2D, and that specific monitoring for CVD, rather than just glycaemia, may be indicated. In contrast, microvascular risk only seems to emerge in those who develop T2D.

Retnakaran R, Shah BR (2017) Role of type 2 diabetes in determining retinal, renal, and cardiovascular outcomes in women with previous gestational diabetes mellitus. *Diabetes Care* **40**: 101–8

Diabetes Care

CV outcomes in people with varying kidney function receiving sitagliptin

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 TECOS, the mandatory safety study of sitagliptin, showed that the agent had a neutral effect on cardiovascular outcomes in people with T2D compared with placebo.

2 In this *post hoc* analysis of TECOS, the authors evaluated the effects of sitagliptin according to baseline kidney function.

3 CV and renal outcomes were evaluated over a median follow-up of 3 years in 14 525 participants, all with T2D and high CV risk, from the intention-to-treat analysis.

4 Participants were categorised according to estimated glomerular filtration rate (eGFR) stages 1, 2, 3a, or 3b (≥90, 60–89, 45–59 or 30–44 mL/min/1.73 m^2, respectively).

5 Four-point major adverse cardiac event (MACE) rates increased in line with decreasing eGFR. Compared with people with stage 1 eGFR, people with stages 3a and 3b had hazard ratios of 1.28 (95% confidence interval [CI], 1.10–1.49) and 1.39 (95% CI, 1.13–1.72), respectively. MACE risk was not significantly different in people with stage 2 eGFR.

6 Sitagliptin was not associated with CV outcomes at any eGFR stage (P>0.44 for all interactions), and kidney function declined at similar rates in both treatment groups.

7 The authors conclude that, in terms of CV outcomes, sitagliptin is safe, although not beneficial, in people with T2D and chronic kidney disease up to stage 3b.

Cornel JH, Bakris GL, Stevens SR et al (2016) Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. *Diabetes Care* **39**: 2304–10

"Statins are still indicated to reduce cholesterol; however, physicians should be aware that intensification of diabetes therapy may be required."

References from commentary

Butalia S, Leung AA, Ghali WA, Rabi DM (2011) Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Diabetol* **10**: 25

Calvin AD, Aggarwal NR, Murad MH et al (2009) Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. *Diabetes Care* **32**: 2300–6

De Berardis G, Sacco M, Evangelista V et al (2007) Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* **8**: 21

De Berardis G, Sacco M, Strippoli GF et al (2009) Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* **339**: b4531

Handelsman Y, Mechanick JI, Blonde L et al (2011) American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract* **17**(Suppl 2): 1–53

Younis N, Williams S, Ammori B, Soran H (2010) Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis. *Expert Opin Pharmacother* **11**: 1459–66

Zhang C, Sun A, Zhang P et al (2010) Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* **87**: 211–8