Aspirin for primary prevention of cardiovascular disease events in diabetes: the balancing act?

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Title Effects of aspirin for primary prevention in persons with diabetes mellitus

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Summary

Diabetes is the fifth leading cause of death in the world, accounting for approximately 3 million deaths annually.[1] Excess mortality in diabetes is largely due to atherosclerotic cardiovascular disease (ASCVD) and renal complications of diabetes. ASCVD encompassing coronary artery disease, peripheral vascular disease and stroke, occurs much more frequently in diabetic than in nondiabetic males and females, but cardiovascular deaths are greater in females.[2] The high prevalence of ASCVD in persons with diabetes is well documented in many populations of the world.[3] Individuals with diabetes have higher atheroma volume, more atherosclerotic plaque and much narrower coronary lumen than do nondiabetics.[4] This makes them at great risk for a much worse myocardial infarction and occurrence of silent myocardial infarction; however, the concept of diabetes as a risk equivalent for established coronary artery disease is still not universally accepted.[5] Efforts to prevent cardiovascular disease in patients with diabetes is a prime requirement to improve the quality of a patient's life and to prevent deaths. Prevention of ASCVD in patients with diabetes involves a multipronged approach, namely control of hyperglycaemia, statin therapy for dyslipidaemia, treatment of high blood pressure and, of course, antiplatelet therapy, especially after a patient has survived a major event such as acute myocardial infarction or stroke.[6] Although secondary prevention of ASCVD with aspirin is well established, the role of aspirin in primary prevention of ASCVD in patients with diabetes is less well established. In the ASCEND (A Study of Cardiovascular Events in Patients with Diabetes) study investigators randomised >15,000 adults who had diabetes but no evident cardiovascular disease to receive 100 mg aspirin or placebo.[7] The primary outcome was the first serious vascular event (i.e. myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial haemorrhage). The primary safety outcome was the first major bleeding event, either intracranial haemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding or other serious bleeding. Secondary outcomes included gastrointestinal tract cancer. After a mean follow up of 7.4 years, the primary outcome (i.e. serious vascular event) occurred in a lower proportion of those who received aspirin with a rate ratio of 0.88 (95% confidence interval: 0.79–0.97). This means that usage of aspirin resulted in 12% lower risk of a serious cardiovascular event; however, there was a 28% higher risk of participants experiencing major bleeding. A total of 314 (4.1%) participants in the aspirin group experienced major bleeding compared to 245 (3.2%) in the placebo group. Major bleeding was gastrointestinal in 41.3%, ocular in 21.1%, intracranial in 17.2% and 20.4% in other sites. Of note, the incidence of fatal bleeding was similar in both the groups; 19 vs 16 participants in the aspirin and placebo groups, respectively. The incidence of gastrointestinal cancer was similar in the two groups.

Opinion

Aspirin is one of the most widely used pharmaceutical agents with antithrombotic properties that has been shown to benefit patients in almost all cardiovascular trials aimed at preventing serious vascular events. There are multiple studies showing the cardiovascular protective effect of aspirin

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in primary preventive trials, as presented in the editorial accompanying the ASCEND trial paper in the *New England Journal of Medicine*.[8] At the same time, there is real risk of bleeding in patients who take aspirin as primary or secondary preventive therapy, and we broadly agree with the authors regarding concerns about safety (bleeding). However, there are certain opinions that we would like to put forth to further understand this trial as well as the use of aspirin in other cardiovascular studies. The dose of aspirin used in diabetic adult patients with no apparent cardiovascular disease in the ASCEND trial was 100 mg, which is slightly higher than doses (75 mg) reportedly used in previous prevention studies.[9] Since aspirin irreversibly inhibits platelet aggregation, the long-term cumulative duration and dose might affect the rate of bleeding events. It is possible that if the authors had used aspirin in lower doses of 75 or 81 mg, there might have been fewer bleeding events. In addition, the use of nonsteroidal anti-inflammatory drugs was slightly higher in the aspirin group than in the nonaspirin group, which may also contribute to increased bleeding events. In the ASCEND trial the benefit of aspirin was demonstrated across all the three vascular risk categories. Though major bleeding occurred more often in the aspirin group, fatal bleeding occurred equally in the aspirin and placebo groups. Another point to be considered is that only 14% of the participants were on proton pump inhibitors (PPIs). Therefore, it is possible that if more participants were on PPIs along with aspirin the gastrointestinal bleeding episodes would have reduced. Furthermore, prediabetes has been shown to be associated with increased cardiovascular risk in many studies and, therefore, it should not surprise us that many patients that we consider low-risk diabetics might actually be silent ticking time bombs.[10] At this time there are no conclusive guidelines about prevention of cardiovascular risk in prediabetes patients other than lifestyle changes and possibly statins. Since diabetes (of any duration and control) is a vascular disease and an angina equivalent, in our opinion, low-dose aspirin should be used to prevent major cardiovascular events in these patients. Since bleeding events in the ASCEND trial were mostly nonfatal, and keeping in mind the huge morbidity and mortality that accompanies an acute myocardial infarction or an acute stroke, we feel that a single low-dose aspirin (75 mg) as primary prevention will produce substantial clinical benefit to the patient with much lower likelihood of bleeding, as opposed to dual antiplatelet therapy that is used after a major cardiovascular event. Remember the dictum ‘prevention is better than cure’.

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