PREVENTION

Aspirin for primary prevention of CVD: a matter of balance

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The long-awaited results of two large trials on the efficacy and safety of daily low-dose aspirin for the primary prevention of cardiovascular disease (CVD), the ASCEND and ARRIVE studies, presented at the 2018 ESC Congress, suggest that the benefit of aspirin in reducing the risk of cardiovascular events in patients at moderate or intermediate risk of CVD does not outweigh the associated increased risk of bleeding.

"The available evidence showed that in high-risk patients (such as those who already have had a heart attack or stroke), the benefits of aspirin outweigh the risks of bleeding, and for healthy people (that is, at low risk) the hazards of aspirin approximately balance the benefits, and so the recommendation is not to treat," explains Jane Armitage, lead author in the ASCEND trial publication on aspirin data. However, limited evidence was available for people with diabetes mellitus, who are at an intermediate risk of CVD. "There had been suggestions that aspirin didn't work in the same way in people with diabetes," she comments. Therefore, Armitage and colleagues set up a large, randomized trial to assess the value of low-dose aspirin for preventing a first event in people with diabetes.

The ASCEND trial included 15,480 patients with diabetes without clinically evident CVD who were randomly assigned to receive 100 mg of enteric-coated aspirin daily or placebo. After a mean follow-up of 7.4 years, a first serious vascular event — myocardial infarction, stroke or transient ischaemic attack, or death from any vascular cause (excluding any confirmed intracranial haemorrhage) — occurred in 8.5% of participants in the aspirin group and 9.6% in the placebo group (rate ratio 0.88, 95% CI 0.79–0.97, $P=0.01$). However, major bleeding events, most commonly gastrointestinal, were more frequent in the aspirin group than in the placebo group (4.1% versus 3.2%; rate ratio 1.29, 95% CI 1.09–1.52, $P=0.003$).

"Aspirin significantly reduced the risk of serious vascular events by 12% but also significantly increased the risk of bleeding by 29% so that, overall, the excess of bleeding approximately counterbalanced the benefits from avoiding serious vascular events," explains Armitage. "We could not identify any group where the benefits clearly outweighed the risks," she adds.

"The ASCEND results provide diabetes guideline committees with long-overdue, high-quality evidence on the efficacy and safety of low-dose aspirin in this setting to support or revise current treatment recommendations," remarks Carlo Patrono, who was not involved in either ASCEND or ARRIVE.

The ARRIVE trial found no benefit of daily aspirin for preventing major cardiovascular events in patients considered to be at a moderate risk of CVD. In total, 12,546 participants with an estimated moderate risk of a first cardiovascular event (defined as 10–20% 10-year risk of coronary heart disease) were randomly assigned to receive 100 mg of enteric-coated aspirin daily or placebo. Patients with diabetes or at high risk of bleeding were excluded. Median follow-up was 5 years. In the intention-to-treat analysis, the rate of the primary end point (a composite of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischaemic attack) was similar in the aspirin and in the placebo groups (4.3% versus 4.5%; HR 0.96, 95% CI 0.81–1.13, $P=0.6038$). By contrast, gastrointestinal bleeding was more frequent with aspirin than with placebo (1.0% versus 0.5%; HR 2.11, 95% CI 1.36–3.28, $P=0.0007$). Nevertheless, the cardiovascular event rates were much lower than expected in the trial design calculation, which the trial investigators suggest is reflective of the increasing use and more effective risk management of contemporary strategies; therefore, the trial was not powered to detect moderate treatment effects. Of note, the use of other cardioprotective treatments was also highly common in the ASCEND trial, with the majority of participants taking statins and antihypertension drugs.

Neither of the trials reported an effect of low-dose aspirin on the incidence of gastrointestinal cancers. "We will continue to follow up the participants in the trial to see if any effects emerge," explains Armitage.

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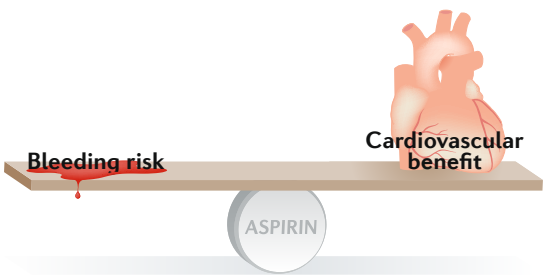

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ORIGINAL ARTICLES The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1804988 (2018) | Gaziano, J. M. et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* https://doi.org/10.1016/S0140-6736(18)31924-X (2018)