Aspirin for primary prevention of cardiovascular disease

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The benefit of aspirin for patients with established cardiovascular disease outweighs the risk of bleeding, but the role of aspirin for individuals with no overt cardiovascular disease is more controversial.[1,2] In a meta-analysis[3,4] of 118 445 individuals from 11 trials of aspirin for primary cardiovascular disease prevention, aspirin reduced the relative risk of non-fatal myocardial infarction by 22% and death by 6%, at the cost of a 59% increase in gastrointestinal bleeding and a 33% increase in haemorrhagic stroke. This compromise in bleeding complications has called into question the level of baseline cardiovascular disease risk for which use of aspirin in primary prevention is clinically acceptable. Indeed, in patients at low cardiovascular disease risk, the relative benefit of aspirin translates into marginal absolute benefit, making its use largely unjustifiable. To better define the net benefit of aspirin for primary prevention, four more trials were designed to include individuals at higher cardiovascular disease risk: two of patients with diabetes (ASCEND and ACCEPT-D), one of patients of advanced age (ASPREE), and one of patients at moderate cardiovascular disease risk (ARRIVE; appendix).[2] J Michael Gaziano and colleagues[5] now report the results of ARRIVE in *The Lancet*.

In ARRIVE, 12 546 patients were randomly assigned to receive either low-dose (100 mg) aspirin or placebo tablets once daily, at 501 sites in seven countries. Inclusion criteria included several major cardiovascular disease risk factors, to target a final population at moderate (ie, 20–30%) risk of 10-year cardiovascular disease. Patients with a history of a vascular event or diabetes were excluded. The primary endpoint was a composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, stroke, unstable angina, or transient ischaemic attack, with a median follow-up of 5 years. In the intention-to-treat analysis, there was no significant difference in the primary endpoint, which occurred in 269 (4·29%) of patients in the aspirin group and 281 (4·48%) of patients in the placebo group (hazard ratio [HR] 0·96, 95% CI 0·81–1·13; p=0·6038). There was a lower HR for aspirin in the per-protocol analysis (0·81, 0·64–1·02; p=0·0756), paralleled by a significant reduction in fatal or non-fatal myocardial infarction and no effect on mortality. Gastrointestinal bleeding events were mostly mild and approximately two times higher in the aspirin group in the intention-to-treat population (HR 2·11, 1·36–3·28; p=0·0007).

Some trial aspects are noteworthy and challenge interpretation of the results. The trial was originally designed under the assumption of a projected 13·4% event rate in the placebo group. Because of the lower than anticipated event rate, the investigators expanded the initial primary endpoint to include unstable angina and transient ischaemic attack, modified the study design from event-driven to time-driven, and extended the time of observation. Still, the final number of events was considerably lower than anticipated, based on the calculated risk profile of the intended population (550 *vs* 1488). The investigators acknowledge that a proportion of events might have been undetected because of ascertainment issues. As such, despite the merits of this relatively large randomised, double-blind, placebo-controlled trial and the attempts to enrich the event rates, it ultimately did not address the role of aspirin in patients with at least moderate cardiovascular disease risk, because the study was primarily done with patients at low risk. Also notable is the high number of participants who prematurely terminated the study (approximately a third in both groups). Because crossovers were not tracked and non-compliance to the study allocation was only patient-reported, the results of both the intention-to-treat and per-protocol analyses should be interpreted with caution, particularly in the context of their diverging results and lower than anticipated statistical power.

The optimal dosing of aspirin has been a subject of debate.[6] Notably, another study published this year, in *The Lancet*, questions the efficacy of fixed low doses of aspirin for primary prevention in patients of different bodyweight categories.[7] With minimum and maximum bodyweights of 43 kg and 177 kg reported in the placebo group of ARRIVE, whether the same neutral results would be replicated by tailoring the dose of aspirin according to bodyweight remains a matter of interest. Weight-stratified analyses of cardiovascular disease events in the ARRIVE trial are planned. Despite also being designed as one-dose-fits-all trials, important lessons can be learned from two ongoing studies of aspirin for secondary prevention, in

which twice-daily versus once-daily (ANDAMAN) and high-dose versus low-dose (ADAPTABLE) strategies are being investigated (appendix). Finally, a key question is whether there is a protective effect of aspirin in cancer prevention (not reported in ARRIVE), for which longer-term follow-up than that reported by the ARRIVE investigators (ie, >10 years) is necessary.[8]

There are important take-home messages from the ARRIVE trial. First, the overall findings replicate those from previous studies testing the use of aspirin for primary prevention in patients at low cardiovascular disease risk. On the one hand, these study findings reinforce recommendations against the use of aspirin in this setting but, on the other hand, leave unanswered the role of aspirin for primary prevention in patients without diabetes who have at least moderate cardiovascular disease risk. To this extent, the European guidelines do not recommend using antiplatelet therapy in individuals without cardiovascular disease because of the increased risk of major bleeding,[9] whereas the US Preventive Services Task Force advocates initiating aspirin on the basis of age and a 10-year cardiovascular disease risk of at least 10%, as defined by available risk estimators.[10] Second, this study highlights the weakness and over-estimation of current methods to define the 10-year risk of cardiovascular disease, which are still based on historical data, underscoring the need for more reliable and contemporary estimates of cardiovascular risk. Finally, the study provides insight into the challenge of doing pragmatic trials of aspirin in an era characterised by other preventive and therapeutic interventions. Overall, the consistent trend in negative results from trials of aspirin in primary prevention, particularly in patients without diabetes, suggests that new avenues of research are needed for the prevention of cardiovascular events.

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