Aspirin for secondary prevention of cardiovascular disease

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The antithrombotic efficacy of low-dose aspirin is well established. Its primary clinical effect is mediated by inhibition of platelet cyclooxygenase-1, which reduces thromboxane A2 formation and inhibits platelet aggregation. Over the course of recent decades, aspirin administration has shown a favourable risk–benefit ratio for reducing the risk of adverse events in patients with known atherosclerotic disease.[1,2] By contrast, in patients without known atherosclerotic disease who are at risk of cardiovascular disease, the overall benefits of aspirin in terms of primary prevention of atherothrombotic events do not outweigh the risk in terms of bleeding.[2,3]

In patients with known coronary, carotid, or peripheral arterial disease, alternative antiplatelet agents such as $P2Y_{12}$ inhibitors are more potent than aspirin and might be preferable. In *The Lancet*, Mauro Chiarito and colleagues[4] report the results of a meta-analysis of randomised trials comparing $P2Y_{12}$ inhibitor therapy with aspirin therapy for secondary prevention of cardiovascular events. A total of nine trials and 42 108 patients were included. The authors report that the mean age of included patients was 63·6 years and 67·4% were men. The main finding was that patients who received a $P2Y_{12}$ inhibitor had a borderline reduction in the risk of myocardial infarction compared with those who received aspirin (odds ratio 0·81 [95% CI 0·66–0·99]; I^2=10·9%), which was of uncertain clinical relevance—the number needed to treat to prevent one myocardial infarction with $P2Y_{12}$ inhibitor monotherapy was 244. The other primary endpoints (risks of stroke, all-cause death, and vascular death) did not differ between patients who received a $P2Y_{12}$ inhibitor and those who received aspirin.

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The analysis was well executed, and the results are relevant to the general discussion regarding the optimal antithrombotic therapy in patients with stable cardiovascular disease. The main strength in comparison with previous analyses is that the study incorporates evidence not only with clopidogrel and ticlopidine, but also with ticagrelor.[1] The results appeared to be consistent with all three drugs.

However, a number of limitations must be considered when interpreting the results. First, most of the included trials were completed many years ago. Only three of the nine included trials were published in the past 5 years. This limits the external validity of the observations. Second, the included trials targeted patient populations with various clinical manifestations of atherosclerosis, and initiated study treatment at different time intervals from the qualifying vascular event. In this respect, it is notable that sensitivity analyses did not identify evidence of interaction with either factor. Third, one particular study—the CAPRIE[5] trial—had a high relative weight, and omission of this trial affected the results of the analysis. Arguably, this trial on its own represents the best evidence for the comparison of the two antiplatelet therapies for secondary prevention. Fourth, the quality of the evidence on bleeding was not high—due to limitations of the data available from individual trials. Although the authors found no difference between the two treatments with respect to overall or major bleeding, the analysis does not provide robust evidence on this important element of the treatment effect. Nevertheless, the observed lower risk of gastrointestinal bleeding with $P2Y_{12}$ inhibitor monotherapy could be important information for patients with heightened risk of this complication. Finally, testing for an interaction of age or sex on treatment effects was not done.

The implications of the findings for clinical practice are a matter of some discussion. Our impression is that the absence of substantial difference between the two approaches supports the use of aspirin—the drug is easier to take, associated with less non-compliance, fewer off-target side-effects (compared with ticagrelor in particular), and less variation in treatment response

(compared with clopidogrel), and is likely to be more cost-effective.

In fact, in the broader context, it could be noted that aspirin monotherapy remains the standard-of-care for secondary prevention of cardiovascular disease. Efforts to either replace aspirin with other antiplatelet agents (as shown in the analysis of Chiarito and colleagues)[4] or improve on its efficacy and safety profile by adding a $P2Y_{12}$ inhibitor[6,7] or a low-dose anticoagulant[8] have not produced results convincing enough to induce a major change in guideline recommendations. Guidelines from the European Society of Cardiology[9] updated in 2019 continue to recommend aspirin as the drug of choice for secondary prevention in patients with chronic coronary syndrome, particularly those with prior myocardial infarction and revascularisation. In these guidelines, clopidogrel is recommended as an alternative and makes sense in patients with aspirin intolerance or heightened risk of gastrointestinal bleeding.

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Psoriatic arthritis: still room for improvement

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Psoriatic arthritis is a complex and heterogeneous inflammatory disease, characterised by diverse clinical manifestations. Patients might have musculoskeletal manifestations—ie, peripheral or axial arthritis, enthesitis, dactylitis, and tendinitis—but non-musculoskeletal involvement is also prevalent—eg, nails, gut, and eyes, in addition to latent or manifest psoriasis.[1] Additionally, patients with psoriatic arthritis have increased risk of cardiovascular, psychological, and metabolic comorbidities.[2] Psoriatic arthritis was thought to be rare, but occurs in up to 30% of patients with psoriasis.[3] Initially considered a benign disease, it is now recognised that disease burden is high and patients have severely reduced quality of life and increased mortality.[4]

Treatment of patients with psoriatic arthritis aims to maximise health-related quality of life through control of symptoms, prevention of structural damage, and normalisation of function and social participation.[5] A cornerstone to achieving these goals is control of the inflammatory process using disease-modifying antirheumatic drugs (DMARDs). International recommendations, most recently from the European League Against Rheumatism (EULAR), provide a strategy for pharmacological therapies.[5] Non-steroidal anti-inflammatory drugs (NSAIDs) and local glucocorticoid injections are proposed as initial therapy for psoriatic arthritis; for patients with arthritis and poor prognostic factors, rapid initiation of conventional synthetic (cs) DMARDs (eg, methotrexate, sulfasalazine, and leflunomide) is recommended. If the treatment target is not achieved with this strategy, biological DMARDs that target different cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-12 or IL-23, and IL-17A, should be initiated, taking into account the involved domains, such as axial or skin disease.[5] Targeted synthetic DMARDs that inhibit phosphodiesterase-4 or Janus kinases have also been added to the available drugs.

A challenge for clinicians is that the safety and efficacy of therapies for psoriatic arthritis have been documented in randomised controlled trials, with placebo as the reference. Head-to-head studies of different drugs are needed to guide clinical decision making regarding the best choice of treatment.[5]