MANUSCRIPT

The recommendations for aspirin use in the primary prevention of cardiovascular disease (CVD) in Australians at elevated risk have changed over time as the body of literature informing them grows. Current practice is largely against prescribing primary preventative aspirin, however, the recent review of the American Diabetes Association (ADA) cardiovascular standards of medical care in diabetes suggests it is time this were reviewed¹.

The issue is complicated by multiple studies with inconsistent findings across risk groups². Of the 11 published randomised control trials (RCTs) of aspirin for CVD primary prevention in high-risk individuals, the current Australian cardiovascular risk modification guidelines published in 2012 by the National Vascular Disease Prevention Alliance considered results from 9³. They state that “Aspirin or other antiplatelet therapy is not routinely recommended for primary prevention of CVD” (a Grade B recommendation) including for high-risk patients, defined as a “>15% absolute risk of CVD events over 5 years”³.

The HOT trial (1998) is the only one of the 11 referred to above that achieved its primary outcome of a reduction in 3-point major adverse cardiovascular events (MACE). However, 6 of the trials showed a statistically significant reduction in non-fatal myocardial infarction (MI). A 2016 meta-analysis including all of these trials showed an overall relative risk (RR) of 0.78 (95% CI 0.71-0.87, p=0.005) for aspirin use vs. placebo for non-fatal MI⁴. Subgroup analysis by risk level found that aspirin use in patients at an 8.44% absolute risk of CVD events over 10 years (the highest risk group considered) prevented 1.43 events per 1000 patient-years, or a number needed to treat of 70 over 10 years. Analysis of the same data found that aspirin caused 1.39 major bleeding events (resulting in death, hospitalisation, transfusion, or described as serious by investigators) per 1000 patient-years, or a number needed to harm of 72 over 10 years⁵.

On the strength of these data the ADA recommends “Aspirin therapy... may be considered as a primary preventative strategy in those with type 1 or type 2 diabetes who are at increased cardiovascular risk” (a Grade C recommendation)¹. The United States Preventative Services Taskforce goes further and recommends that clinicians should “initiate low-dose aspirin” (a Grade B recommendation) in adults 50-59 years with a $\geq 10\%$ 10-year CVD risk; this can be considered in the 60-69 age group (a Grade C recommendation)⁶.

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Aspirin increases both non-fatal and fatal bleeding and this must be considered in any patient before commencing^{2,5}. However, we may be missing an opportunity to prevent many non-fatal MIs, an important cause of morbidity in a high-risk population, with a cheap and acceptable intervention. It is time our guidelines were reviewed.

Since the submission of this letter for publication three modern trials of primary preventative aspirin have been published. Aspirin was associated with no cardiovascular benefit in the elderly but low-risk (3.45-3.88% 5-year event-rate) ASPREE population (hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.83-1.08, $p>0.05$) or the low-to-moderate-risk (4.29-4.48% 5-year event-rate) ARRIVE trial (HR 0.96, 95% CI 0.81-1.13, $p=0.604$)^{7,8}. The high-risk (8.5-9.6% 7.4-year event-rate) ASCEND trial did show a benefit (RR 0.88, 95% CI 0.79-0.97, $p=0.01$), but at the cost of increased major bleeding (RR 1.29, 95% CI 1.09-1.52, $p=0.003$)⁹. This large modern dataset studied in the context of widespread statin use, falling smoking rates, and increasing use of diabetes agents that modify cardiovascular risk is invaluable to our understanding of primary preventative aspirin use and serves only to strengthen the need for guidelines to be updated.

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ABSTRACT

Aspirin for cardiovascular disease primary prevention is recommended against by relevant Australian guidelines. The body of evidence and international guidelines support its use to prevent non-fatal myocardial infarctions in patients at high cardiovascular risk. The Australian guidelines, now 6 years old, should be reviewed and updated to reflect latest evidence.

TITLE PAGE

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Aspirin for cardiovascular disease primary prevention is recommended against by relevant Australian guidelines. The body of evidence and international guidelines support its use to prevent non-fatal myocardial infarctions in patients at high cardiovascular risk. The Australian guidelines, now 6 years old, should be reviewed and updated to reflect latest evidence.

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