When Should Aspirin Be Used for Prevention of Cardiovascular Events?

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With more than 100 years of use, aspirin is one of the most extensively studied drugs in the history of medicine. In addition to its analgesic, anti-inflammatory, and antipyretic effects, acetylsalicylic acid is a potent irreversible inhibitor of platelet aggregation. In the late 19th century the acetylation of salicylic acid in an attempt to make it less bitter and hence more palatable inadvertently gave this compound a unique property—the acetyl group can be transferred to the serine residue in the active site of the enzyme cyclooxygenase (COX), irreversibly inhibiting its function and thereby preventing the production of prostaglandins.

In certain cells this property of aspirin is responsible for analgesic, anti-inflammatory, and antipyretic effects. In platelets, the COX-1 isoform produces thromboxane A₂, which aids in platelet aggregation. Thus, aspirin inhibits platelet aggregation and can reduce thrombosis. In cells with a nucleus, COX can be regenerated. Because platelets have no nucleus, COX-1 cannot be reproduced and is permanently inhibited. This leads to a prolonged antithrombotic effect lasting several days after a single dose until enough new platelets have been produced to restore normal function of the thrombotic system.

With this unique property, aspirin has valuable therapeutic effects in reducing the risk of arterial vascular thrombotic events, such as myocardial infarction and stroke, and, to a lesser extent, venous thrombotic events. However, this action of aspirin also increases the risk of bleeding, leading to its most troubling adverse effects: serious gastrointestinal bleeding and hemorrhagic stroke. Overall, the balance between benefit in preventing major vascular events and the risk of increasing serious bleeding events underlies the clinical decision of when to use this inexpensive generic drug. In general, the higher the risk of vascular events, the more advantageous it is to prescribe aspirin.

A single trial, ISIS-2,⁴ demonstrated the utility of daily aspirin in the setting of acute myocardial infarction reducing the risk of vascular death by 23%. Aspirin also has been shown to be effective in the setting of acute ischemic stroke.⁵ The acute benefits of aspirin in aiding in the dissolution of an acute thrombus over hours to days and thus restoring blood flow in the setting of stroke or myocardial infarction vastly outweigh any short-term bleeding risks. For this reason, aspirin is a mainstay of early therapy in the acute settings of acute coronary syndromes and stroke.

In pooled data from about 200 trials among patients with known vascular disease, aspirin was shown to have long-term benefits in preventing major vascular events.⁶ These trials demonstrated that among those with known vascular disease there is net benefit, reducing the risk of major vascular events by more than 20% exceeding the modest bleeding risks when aspirin is taken at a low dose daily. Higher doses do not increase the beneficial effects but increase the risk of bleeding. Thus, aspirin is recommended at a dose of 75 mg to 100 mg per day for longer-term secondary prevention of cardiovascular events in patients with known vascular disease. Aspirin also has utility in the setting of vascular procedures such as percutaneous coronary interventions, reducing the risk of restenosis, and is recommended for several months up to a year after the procedure.

Given the beneficial effects of aspirin during acute events, following procedures, and in the secondary prevention of major vascular events among patients with cardiovascular disease (CVD), it was logical to ask whether this inexpensive drug could prevent the first myocardial infarction or stroke among persons who have yet to manifest vascular disease. Primary prevention trials for this question are especially challenging given the continued reduction in the incidence of important outcomes and require very large study populations followed up for many years.

Beginning in the 1980s several large-scale trials were undertaken to address this question, starting with 2 trials among male physicians, the British Doctors’ Trial³ and the Physicians’ Health Study.⁴ These studies, along with a handful of other primary prevention trials among more than 100 000 study participants, have generally shown more modest reductions of major vascular events compared with secondary prevention (12% for major vascular events vs 22% for secondary prevention⁷,⁸) and reductions in myocardial infarction and transient ischemic attack risk, and some have demonstrated a reduced risk of ischemic stroke.⁵,⁶

In the vast majority of the primary prevention trials, the overall risk level of CVD events was very low.³ In the primary prevention setting, there are limited data among those at higher risk. There is also a paucity of data in Asian populations, in which hemorrhagic stroke risk (one of the important adverse effects of aspirin) tends to be higher than in Western populations, and thus this population is of particular interest.

In this issue of JAMA, Ikeda and colleagues⁹ report the results of the Japanese Primary Prevention Project (JPPP). The JPPP clinical trial studied the effect of once-daily, low-dose (100 mg), enteric-coated aspirin compared with no aspirin for preventing atherosclerotic events in 14 658 Japanese patients 60 years or older with hypertension, dyslipidemia, or diabetes. The study, which had planned to follow up participants for 6.5 years, was stopped early due to futility. After a median follow-up of 5 years, there was no significant difference in the rate of the composite primary end point of total number of major atherosclerotic events (nonfatal myocardial infarction, non-
fatal stroke, CVD death), with a cumulative composite event rate of 2.77% in the aspirin group and 2.96% in the no aspirin group (hazard ratio [HR], 0.94 [95% CI, 0.77-1.15]). There were reductions in prespecified secondary end points of myocardial infarction and transient ischemic attack, but increased risk of serious bleeding events. These results are consistent with those of other primary prevention trials, except that in JPPP the overall risk of intracranial hemorrhage appeared higher in the studied Asian population than in Western populations. In fact, in this population, there were more fatal and nonfatal hemorrhagic strokes than myocardial infarctions.

Although study participants were older than 60 years and had CVD risk factors, the event rate was much lower than expected, leading to a study with less power to detect differences in the primary outcome than anticipated. The study was designed to detect a 20% relative difference (ie, based on a revised power estimate using revised assumptions, the authors anticipated a reduction in the annual frequency of events from 0.87% with no aspirin to 0.70%), which is larger than the composite 12% reduction seen in pooled primary prevention studies. Several other limitations are worth noting. The study was not blinded and did not have a placebo control due to Japanese ethical standards, and the drop-in rate and rate of patients lost to follow-up were about 10%. The role that enteric coating might have on the efficacy of low-dose aspirin is not clear.

Aspirin primary prevention trials have become increasingly challenging to conduct. There is wider use of a number of prevention medications such as antihypertensive agents and lipid-lowering drugs, as well as other preventive measures that collectively result in fewer events than expected, as seen in JPPP. In addition, aspirin may be started in some patients who develop evidence of vascular disease before developing a major outcome. This selective drop-in may be even more of an issue in an unblinded study. In JPPP, nearly 10% of patients in the no aspirin group began using aspirin by the end of the study. Also, self-reported adherence with taking aspirin was only 76% among those who attended study visits. There was also a substantial rate of loss to follow-up, and it is possible that those who experienced events could have been lost to follow-up at a higher rate than those without events. This could have reduced the overall observed event rate. Although these issues present challenges for the conduct of long-term trials, they reflect the real practice of medicine in the 21st century.

The JPPP study adds to the body of evidence that helps refine the answer to the question of when aspirin should be used to prevent vascular events. Decision making involves an assessment of individual risk-to-benefit that should be discussed between clinician and patient. However, at present the choice of aspirin remains clear in several situations. Aspirin is indicated for patients at high short-term risk due to an acute vascular event and those undergoing certain vascular procedures; patients with any evidence of vascular disease should be given daily aspirin. On the other hand, patients at very low risk of vascular events should not take aspirin for prevention of vascular events, even at low dose.

However, some individuals who do not have overt vascular disease will have risk levels that approach those of patients with CVD (such as patients with multiple risk factors). It remains likely that there is some level of risk of CVD events that would result in a positive trade-off of benefit and risk for the use of aspirin, but the precise level of risk is uncertain. This is in part because most populations studied have been at very low risk. Patients at higher than average risk are being studied in 3 ongoing trials of aspirin in primary prevention. The ASCEND study involves aspirin for patients 40 years and older with type 1 or 2 diabetes; the ARRIVE study is testing aspirin in middle-aged and older patients who are at higher risk based on the presence of multiple CVD risk factors; and the ASPREE study is testing aspirin in individuals older than 70 years.

Information from these studies will help refine guidelines that currently reserve aspirin for higher-risk patients. Findings from these studies, with additional data about risks and other potential long-term benefits, such as reducing the risk of colorectal and other cancers, will prove helpful for clinical decision making involving the role of aspirin for primary prevention.

### REFERENCES