Primary Prevention of Cardiovascular Complications – the Role of Low-Dose Aspirin

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Fifty years ago, a California physician noticed that tonsillectomy patients who took a chewable form of aspirin for pain relief had an unusually high occurrence of bleeding. He theorized that this side effect might have a beneficial application in preventing blood clots that led to heart attacks. By1971, researchers had found the mechanism underlying his observation. In platelets, small amounts (50-100 mg/day) of aspirin irreversibly acetylate the active site of cyclooxygenase, which is required for the production of thromboxane A_2, a powerful promoter of platelet aggregation. This effect persists for the entire life of the platelet and is so pronounced that higher doses of aspirin appear to yield no additional protection.

The benefits of aspirin in the secondary prevention of cardiovascular disease (CVD) have been conclusively demonstrated. In their third meta-analysis, the Antithrombotic Trialists' Collaboration reviewed 287 trials, including 194 that randomized 135,000 patients comparing antiplatelet therapy, particularly aspirin at various doses, with placebo, and 93 that randomized 77,000 patients comparing various antiplatelet regimens to each other. Compared with placebo, those assigned to aspirin or other antiplatelet agents had an approximately 22 percent reduction in the combined outcome of any serious vascular thrombotic event (non-fatal MI, non-fatal stroke or vascular death) and had clear reductions in MI (34%), Stroke (25 %) and vascular death (15%). Antiplatelet therapy was protective in a wide range of high-risk patients, including those with acute MI or stroke; previous MI, stroke, or transient cerebral ischemia; unstable or stable angina; peripheral artery disease; or atrial fibrillation. This meta-analysis indicated clear benefits at doses of aspirin higher than 75 mg per day and uncertain affects of aspirin at lower doses. Consequently, unless contraindicated, aspirin should be used by those with known CVD at a dose of at least 75 mg per day.

The risk/benefit analysis is more complicated for those at risk of an initial cardiovascular event. By 1988, findings from the aspirin arm of the landmark Physicians' Health Study indicated that prophylactic aspirin was effective in reducing the risk of a first myocardial infarction. Four other large-scale trials, largely limited to men, and one large-scale trial in women have now assessed the benefits of low-dose aspirin in the prevention of cardiovascular disease. The first five studies were conducted primarily in men. Taken together, these studies, which included over 55,000 participants, indicate a benefit of prophylactic aspirin in the primary prevention of CVD. However, concerns regarding increased risk of hemorrhagic stroke have not yet been fully assessed. The recently published data from the Women's Health Study, the only trial specifically involving women and the only primary prevention trial using a dose (100 mg every other day) under 75 mg of aspirin daily, demonstrated that aspirin lowered the risk of stroke with less clear results for MI or death from cardiovascular causes. The exception was among women 65 or older; those who took aspirin saw significant reductions in major CVD events, MI and stroke compared to those who took placebo. Further, smoking seemed to reduce the benefits of aspirin at this dose.

In summary, those with documented CVD should be on aspirin at a dose of at least 75 mg per day unless clearly contraindicated. In primary prevention, the use of aspirin for prevention must take into account the individual's long-term risk of subsequent cardiovascular disease. Currently, the U.S. Preventive Services Task Force recommends aspirin for adults whose 10-year risk of a coronary heart disease event is 6 percent or greater; the American Heart Association recommends aspirin for adults whose 10-year risk is at least 10 percent. These recommendations may be revised as more data become available by pooling all the primary prevention trials and from special populations that are currently under study.

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