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AHA Scientific Statement

Aspirin as a Therapeutic Agent in Cardiovascular Disease

A Statement for Healthcare Professionals From the American Heart Association

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Cardiovascular disease, which includes myocardial infarction, stroke, and peripheral vascular diseases, is the leading cause of death in the United States and most developed countries, accounting for more than 900,000 deaths annually in the United States alone. Aspirin can reduce risks of occlusive vascular events by inhibiting platelet aggregation, but uncertainty among healthcare providers remains regarding its appropriate use in different categories of patients. This concise review of current knowledge, an update of an earlier AHA statement, is intended to provide clinicians with guidelines for the use of aspirin in the treatment and prevention of cardiovascular disease.

Acute Myocardial Infarction

Aspirin therapy confers conclusive net benefits in the acute phase of evolving myocardial infarction (MI) and should be administered routinely to virtually all patients with evolving acute MI. In the Second International Study of Infarct Survival (ISIS-2) more than 17,000 men and women within 24 hours of onset of symptoms of suspected MI were randomly assigned to 162 mg of aspirin or placebo daily for 30 days. After 5 weeks patients allocated to receive aspirin had statistically significant reductions in risk of vascular mortality (23%), nonfatal reinfarction (49%), and nonfatal stroke (46%). There was no increase in hemorrhagic stroke or gastrointestinal bleeding in the treated group and only a small increase in minor bleeding. Thus, aspirin has perhaps the best benefit-to-risk ratio of any proven therapy for acute MI. The benefits of aspirin on risk of subsequent MI, stroke, or vascular death are substantial and the risks of serious bleeding and sensitivity reactions low as well as amenable to treatment in an acute care setting, even with a history of bleeding or other sensitivity to aspirin. Thus, contraindications to use of aspirin in acute MI are relative, not absolute.

To achieve an immediate clinical antithrombotic effect, an initial minimum loading dose of 162 mg should be used in acute MI. If an enteric-coated aspirin is the only preparation available, the first tablet should be chewed or crushed before

administration. In 1996 the US Food and Drug Administration (FDA) proposed a professional labeling indication for aspirin in patients with acute MI: an initial dose of 160 to 162.5 mg to be continued daily for at least 30 days.

Despite its clear benefits in this clinical setting, aspirin as a treatment for acute MI remains underused. In 1993 in a national registry of more than 1000 large US hospitals, only 77% of patients with acute MI received aspirin. In a survey of treatment of Medicare patients in the early 1990's, only 61% of a sample of acute MI patients aged 65 and older were taking aspirin within 2 days of hospitalization. Increased administration of aspirin to virtually all patients with acute MI would save an additional 5,000 to 10,000 lives in the United States each year.

Secondary Prevention

Long-term aspirin therapy confers conclusive net benefits on risk of subsequent MI, stroke, and vascular death among patients with a wide range of prior manifestations of cardiovascular disease. The 1994 Antiplatelet Trialists' Collaboration overview analyzed results of randomized trials of antiplatelet therapy among more than 54,000 high-risk patients with prior evidence of cardiovascular disease. These trials included patients with prior MI, stroke, transient ischemic attacks (TIAs), unstable angina, stable angina, revascularization surgery, angioplasty, atrial fibrillation, valvular disease, and peripheral vascular disease. Among such patients, aspirin therapy reduced by about one quarter the risk of subsequent vascular events (nonfatal MI plus nonfatal stroke plus vascular death). This benefit was separately statistically significant in middle-aged and older patients, men and women, hypertensive and normotensive patients, and diabetic and nondiabetic patients. In absolute terms this benefit translated to avoidance of approximately 50 vascular events per 1000 patients with unstable angina treated for 6 months; 40 events per 1000 patients with prior MI, stroke, or TIAs treated for 2 to 3 years; and 20 events per 1000 patients among other high-risk patients treated for 1 year. The most widely tested regimen in the secondary prevention trials was medium-dose aspirin (75 to 325 mg /d), and in the overall analyses there was no evidence that either higher doses of aspirin or any other antiplatelet regimen was more effective than daily aspirin in this dose range. In the trials of stroke and TIA, higher doses (650 to 1300 mg/d) were used, but in trials of post-MI patients, lower doses (75 to 325 mg/d) appeared equally beneficial in reducing risks of subsequent stroke. Therefore, daily aspirin therapy at a dose of at least 75 to 325 mg should be strongly considered for all such patients at elevated risk of subsequent vascular events. For patients with TIA or stroke, at least 75 to 325 mg a day is indicated, and doses from 650 to 1300 mg/d may be more beneficial" but will produce more side effects. Since publication of the 1994 Antiplatelet Trialists' Collaboration overview, several additional trials have compared other antiplatelet agents with aspirin. In the TASS study, those receiving ticlopidine (500 mg/d) had a 21% decrease in all types of stroke at 3 years compared with those receiving aspirin

(1300 mg/d). The occurrence of neutropenia in almost 1% of patients receiving ticlopidine as well as its additional expense may limit its clinical use. Clopidogrel (75 mg/d) was compared with aspirin (325 mg/d) in a randomized trial of 19,185 patients with recent ischemic stroke, MI, or peripheral arterial disease. Annual rates of the composite outcome of ischemic stroke, MI, and vascular death were 5.83% and 5.32% in the aspirin and clopidogrel groups, respectively ($p=0.043$), with no major differences reported in the safety of the two regimens.

In the 1980s the FDA approved professional labeling indications for aspirin in patients with prior MI and unstable anginal as well as for men with prior TIAs. In January 1997, at a joint meeting of the FDA Nonprescription Drugs and Cardiovascular and Renal Drugs Advisory Committees, members voted to recommend that the FDA expand the professional labeling indication to include women as well as men with prior TIAs and patients with prior occlusive stroke or chronic stable angina.

Primary Prevention

Aspirin has been evaluated in two primary prevention trials. In the US Physicians' Health Study, among 22,071 male physicians, an alternate-day dose of 325 mg of aspirin conferred a statistically significant 44% reduction in risk of first MI. The findings for stroke as well as overall cardiovascular mortality were inconclusive due to inadequate numbers of events, but there was evidence of a possible increase in hemorrhagic strokes in the aspirin group. Although this finding was not statistically significant, any agent that inhibits platelet aggregation may pose a risk of increased bleeding. A British trial, also among male physicians, found no significant effects of aspirin, although it was far smaller in sample size (5139) than the US trial. An overview of the findings from both trials demonstrated a statistically significant 32% reduction in risk of nonfatal MI. Even when the results of the two studies were considered together, the data for stroke and cardiovascular death remained inconclusive.

Additional data in primary prevention are needed for complete assessment of aspirin's benefit-to-risk ratio in apparently healthy persons. Specifically such data would allow clinicians to weigh the clear benefit of aspirin on MI against any risks, including a possible increase in hemorrhagic stroke. Such evidence will be provided by the Women's Health Study, an ongoing trial of administration of low-dose aspirin among approximately 40,000 US female healthcare professionals. Pending the results of this trial, any policy recommendation concerning aspirin in the primary prevention of cardiovascular disease would be premature. The US Preventive Services Task Force has issued a similar statement, concluding that there is insufficient evidence to recommend for or against routine aspirin prophylaxis in primary prevention and that any use should be an individual clinical judgment. While awaiting definitive data from the Women's Health Study, aspirin therapy in primary prevention may be warranted for patients at risk of MI.

However, such use must at present be based on an individual clinical judgment by healthcare providers that takes into account a patient's particular cardiovascular risk profile, the demonstrated benefits of aspirin on reducing risk of a first MI, and known as well as unknown side effects.

Summary

Aspirin therapy is of proven value in treatment of acute MI as well as long-term use in patients with a wide range of prior manifestations of cardiovascular disease. The more widespread use of aspirin in these patient categories will contribute to reductions in cardiovascular disease morbidity and mortality. Additional data are needed from randomized trials in primary prevention, particularly the ongoing Women's Health Study, to formulate rational policy recommendations for use of aspirin in apparently healthy people. In the meantime, use of aspirin in primary prevention of MI should remain an individual clinical judgment. Aspirin therapy should always be an adjunct, not an alternative, to management of other risk factors.

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