# 69. Aspirin Prophylaxis for the Primary Prevention of Myocardial Infarction

*RECOMMENDATION*

There is insufficient evidence to recommend for or against routine aspirin prophylaxis for the primary prevention of myocardial infarction (MI) in asymptomatic persons. Although aspirin reduces the risk of MI in men ages 40–84, its use is associated with important adverse effects, and the balance of benefits and harms is uncertain. If aspirin prophylaxis is considered, clinicians and patients should discuss potential benefits and risks for the individual before beginning its use (see ***Clinical Intervention***).

## Burden of Suffering

Cardiovascular diseases are the leading causes of death in the U.S., with a mortality rate in 1993 of 366.3/100,000 population.[1] There are approximately 1.5 million myocardial infarctions (MIs) annually and nearly 500,000 deaths from ischemic heart disease.[1,2] Each year, about 150,000 Americans die from stroke.[1,2] The cost to the U.S. of medical care and lost productivity due to cardiovascular diseases was estimated at $117.4 billion in 1990.[2] MI and sudden death often occur without warning in persons with no history of angina pectoris or other cardiovascular symptoms. The principal risk factors for coronary heart disease are smoking, high blood pressure, elevated serum cholesterol, obesity, diabetes mellitus, physical inactivity, increased age, male sex, and a family history of premature coronary artery disease. Postmenopausal hormone replacement is associated with reduced risk of coronary heart disease in women (see Chapter 68).

## Efficacy of Chemoprophylaxis

Two randomized controlled trials, one each in the U.S. and Great Britain, have examined the efficacy of aspirin in the primary prevention of MI in healthy middle-aged and older men. In the American trial, more than 22,000 asymptomatic male physicians received either 325 mg aspirin or placebo every other day.[3–5] Physicians ages 40 to 84 years were enrolled, although few subjects were older than 75 years. The study was terminated

prematurely, after 60.2 months of follow-up, when a statistically significant 44% reduction in the incidence of total (fatal plus nonfatal) MIs was noted in the group receiving aspirin. This represents an absolute risk reduction of less than two events per thousand individuals per year. In subgroup analyses, this beneficial effect occurred only in individuals age 50 years and older, although the absolute number of MIs occurring in those under the age of 50 was very small. Total cardiovascular mortality was equal between the two groups (81 in the aspirin group vs. 83 in the placebo group).

The British trial, with a smaller sample size (5139 male physicians ≤80 years of age) and a higher dose of aspirin (500 mg daily), found no significant change in incidence of MI (1% increase) or total cardiovascular mortality (6% reduction) in the treated group.[6] Although the apparent absence of an effect on these outcomes may have been due to lack of efficacy, the British trial may have failed to demonstrate a significant effect due to inadequate sample size or other differences in study design (e.g., high dropout rate, higher dose, no placebo).[7]

In the American physician trial, an increase in sudden death was noted in the aspirin group (22 vs. 12) which offset the reduction in fatal MI, leading to similar rates of total cardiovascular mortality. Both the American and British trials observed an increase in the incidence of stroke among persons taking aspirin, which in the American trial was due primarily to an increase in hemorrhagic stroke.[4] However, none of these differences was statistically significant.[4,6] In addition to possible increases in risk of hemorrhagic stroke and sudden death, other side effects of aspirin therapy must be considered in evaluating its long-term safety. Aspirin can produce unpleasant gastrointestinal symptoms such as stomach pain, heartburn, nausea, and constipation, as well as gastrointestinal blood loss, gastritis, and peptic ulcer disease.[8] The likelihood of these side effects in otherwise healthy persons is directly related to the dose of aspirin.[9] In the British trial, in which the dose was 500 mg daily, 20% of the doctors taking aspirin had to discontinue the drug due to dyspepsia or constipation, 3.6% experienced bleeding or bruising, and 2.2% had gastrointestinal blood loss.[6] In the American trial, in which the dose was 325 mg every other day, there was less than a 1% difference in gastrointestinal complaints between the aspirin and placebo groups. Although the transfusion rate was statistically significantly higher in the aspirin group, only one case (which was unconfirmed) of fatal gastrointestinal hemorrhage was reported in this group in 5 years of treatment.[4] Similarly, a large secondary prevention trial also reported little difference in epigastric discomfort, decreased hemoglobin concentration, or occult blood in stool in persons receiving 325 mg/day.[10]

There are no randomized controlled trials that assess the role of aspirin prophylaxis in the primary prevention of cardiovascular disease in

women, although one such study is currently being conducted among 40,000 U.S. female health professionals over the age of 45.[11] A 1991 prospective cohort study[12] followed 87,678 women (registered nurses) for 6 years to examine the association between self-selected aspirin use and risk of a first MI. After controlling for risk factors, they found a statistically significant association between taking one to six aspirins a week and a 25% reduction in first (nonfatal plus fatal) MI. The association was seen at all ages, but was strongest in women age 50 and older. No benefit was seen for those using 7–14 or 15 or more aspirins per week. Aspirin usage did not affect the rate of hemorrhagic stroke. There was a nonsignificant reduction in total cardiovascular and all-cause mortality in the aspirin group. The association between aspirin prophylaxis and reduction in first MI was accentuated in women who currently smoked, had a history of hypertension, or had an elevated serum cholesterol level.

The success of aspirin prophylaxis in persons who have documented disease (secondary prevention) is felt by some to support the practice of prescribing aspirin in asymptomatic, high-risk persons. Several secondary prevention trials have shown that daily aspirin ingestion can lower the risk of subsequent nonfatal ischemic strokes, nonfatal MI, and total cardiovascular mortality in persons at increased risk for thrombotic cardiovascular events (those with unstable angina, previous MI, transient ischemic attacks, prior ischemic stroke, and after coronary artery bypass graft surgery and thrombolysis).[10,13–17] Three meta-analyses extend the populations for whom aspirin is beneficial for secondary prevention to include women, the elderly, hypertensives, and diabetics.[18–20] Aspirin has also been shown to reduce mortality in acute evolving MI.[14]

The use of aspirin to prevent stroke has also been proposed for persons without neurologic symptoms who are at increased risk for thromboembolic events, including those with carotid bruits (see Chapter 4), valvular heart disease, and atrial fibrillation.[21,28] Some evidence supports the use of aspirin in nonrheumatic atrial fibrillation,[22–26] but convincing data to support its efficacy in persons with valvular heart disease or carotid bruits are lacking. There have been no randomized trials designed to evaluate the role of aspirin in the primary prevention of stroke.

A review of 25 secondary prevention trials with a total of 29,000 patients[27] found little difference in outcome in dosages ranging from 300 to 1500 mg/day, suggesting that lower-dose therapy is as effective as higher dose regimens in reducing cardiovascular risks while reducing the risk of side effects. It is possible that high-dose therapy may even have less platelet-inhibitory effect than low-dose therapy, because of inhibition of vessel wall synthesis of prostacyclin along with platelet production of thromboxane $A_2$.

### Effectiveness of Counseling

There is little information on whether asymptomatic patients will comply with physician advice to take aspirin for an extended period of time. Aspirin is the most consumed drug in the U.S., with an estimated 20–30 billion tablets ingested each year,[10] but most patients use aspirin to relieve pain, fever, or other symptoms. It is not known whether healthy individuals would be able or willing to comply with a lifelong daily (or alternate day) regimen, especially if it produces unpleasant side effects. As noted above, over the course of 6 years, 20% of the doctors participating in the British trial were forced to discontinue a daily 500 mg aspirin regimen because of dyspepsia or constipation. In the American study, 33,223 male physicians were initially willing to participate, but after an 18 week run-in period one third of them (11,152) were excluded prior to randomization because of poor compliance, the development of an exclusion criterion or side effects, or an unwillingness to continue participation. Compliance by physicians may not accurately predict compliance in the general population.

### Recommendations of Other Groups

The American Heart Association has recently stated that the use of aspirin seems prudent in middle-aged and older men whose risks of a first MI are sufficiently high to warrant the possible adverse effects of long-term use of the drug.[28] They emphasize that the decision to use aspirin should be made on an individual basis, that aspirin prophylaxis is only an adjunct to coronary heart disease risk factor management, and that efforts should first be directed at modifying primary risk factors for heart disease and stroke, assessing potential contraindications to aspirin, and counseling patients about potential side effects and symptoms requiring medical attention.[29]

The Canadian Task Force on The Periodic Health Examination states that there is no clear evidence that routine use of aspirin in asymptomatic men leads to a reduction in all-cause mortality, cardiovascular disease, or MI (when sudden deaths are taken into account). They concluded that the evidence was not strong enough to support a recommendation for or against routine aspirin therapy for the primary prevention of cardiovascular disease in asymptomatic men and women. The Canadian Task Force recommended that the decision whether to prescribe aspirin should be made on an individual basis after the benefits of decreased risk of ischemic cardiovascular events have been balanced against the potential risks associated with prolonged aspirin use.[30]

The American Academy of Family Physicians recommends that physicians discuss aspirin prophylaxis with men who have risk factors for MI (e.g., high blood cholesterol, smoking, diabetes mellitus, family history of early-onset coronary artery disease) and who lack a history of gastroin-

testinal or other bleeding problems and other risk factors for bleeding or cerebral hemorrhage.[31] This policy is currently under review.

## Discussion

Data from a large trial have provided evidence that low-dose aspirin therapy can reduce the risk of MI in asymptomatic men.[4] However, it is important to note that these benefits were demonstrated in a select population: male doctors between the ages of 40 and 84, in exceptionally good health, who were prescreened to eliminate persons unable to tolerate aspirin. In addition, there was no benefit in total cardiovascular mortality, because the reduction in the rate of acute fatal MI was offset by an increased rate of sudden death. No study to date, however, has had sufficient power to adequately evaluate the effectiveness of low-dose aspirin in reducing total cardiovascular mortality. Some patients might judge the reduced risk of nonfatal MI inadequate to justify the increased complication rates associated with aspirin prophylaxis. In both the U.S. and British studies, significant complications including duodenal ulcers and gastrointestinal bleeding were noted in the aspirin group. Moreover, in both trials, strokes were more common in men taking aspirin. Although the differences were not statistically significant, the consistency of the findings suggests that further study of the relationship between aspirin therapy and cerebral hemorrhage is warranted. Some have suggested that hypertensive patients, a population at increased risk for both coronary artery and cerebrovascular disease, may be more likely to experience hemorrhagic stroke while taking this drug.[10,32]

## *CLINICAL INTERVENTION*

There is insufficient evidence to determine whether the proven benefits of routine aspirin prophylaxis given for the primary prevention of MI in asymptomatic men ages 40 to 84 years outweigh the proven harms, and thus the U.S. Preventive Services Task Force does not recommend for or against its use (“C” recommendation). In men with other risk factors for coronary heart disease who lack contraindications to aspirin use (including allergy to aspirin, history of uncontrolled hypertension, liver or kidney disease, diabetic retinopathy, peptic ulcer or other gastrointestinal disease, bleeding problems, or other risk factors for bleeding or cerebral hemorrhage), the benefits may outweigh the harms. In asymptomatic men without risk factors for coronary heart disease or with relative contraindications to aspirin use, the harms may outweigh the benefits. If aspirin therapy is considered, physicians and patients should understand the potential benefits and risks of aspirin therapy before beginning treatment. At the present time, data are insufficient to support or oppose the

use of aspirin prophylaxis for the prevention of MI in women ("C" rec - ommendation). All patients should be encouraged to focus their efforts on modifying primary risk factors for cardiovascular disease such as smoking (Chapter 54), elevated cholesterol (Chapters 2 and 56), and hypertension (Chapter 3).

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Peter W. Pendergrass, MD, MPH, and Carolyn DiGuiseppi, MD, MPH.

REFERENCES

1. National Center for Health Statistics. Annual summary of births, marriages, divorces, and deaths: United States, 1993. Monthly vital statistics report; vol 42 no 13. Hyattsville, MD: Public Health Service, 1994.
2. American Heart Association. 1993 heart and stroke fact statistics. Dallas, TX: American Heart Association, 1993.
3. The Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1988;318:262–264.
4. The Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129–135.
5. Manson JE, Buring JE, Satterfield S, et al. Baseline characteristics of participants in the Physicians' Health Study: a randomized trial of aspirin and beta-carotene in U.S. physicians. Am J Prev Med 1991;7:150–154.
6. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988;296:313–316.
7. Hennekens CH, Peto R, Hutchison GB, et al. An overview of the British and American aspirin studies. N Engl J Med 1988;318:923–924.
8. Fuster V, Cohen M, Chesebro JH. Usefulness of aspirin for coronary artery disease. Am J Cardiol 1988;61:637–640.
9. UK-TIA Study Group. United Kingdom transient ischemic attack (UK-TIA) aspirin trial interim results. BMJ 1988;296: 316–320.
10. Lewis HD, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration cooperative study. N Engl J Med 1983;309:396–403.
11. Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. J Myocardial Ischemia 1992;4: 27–29.
12. Manson JE, Stampfer MJ, Colditz GA, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. JAMA 1991;266:521–527.
13. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–360.
14. Wallentin LC. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. J Am Coll Cardiol 1991;18:1587–1593.
15. The Salt Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. Lancet 1991;338:1345–1349.
16. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991;325:1261–1266.
17. Nyman I, Larsson H, Wallentin L. Prevention of serious cardiac events by low-dose aspirin in patients with silent myocardial ischemia. Lancet 1992;340:497–501.
18. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81–106.

19. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. BMJ 1994;308:159–168.
20. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. BMJ 1994;308:235–246.
21. Foster JW, Hart RG. Antithrombotic therapy for cerebrovascular disease: prevention and treatment of stroke. Postgrad Med 1986;80:199–206.
22. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation study: final report. Circulation 1991;84:527–539.
23. Peterson P, Boyson G, Godtredsen J, et al. Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. Lancet 1989;1:175–179.
24. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992;327:1406–1412.
25. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323:1505–1511.
26. Connolly SJ, Laupacis A, Gent M, et al. Canadian atrial fibrillation anticoagulation (CAFA) study. J Am Coll Cardiol 1991;18:349–355.
27. Anti-Platelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. BMJ 1988;296:320–331.
28. Fuster V, Dyken ML, Vokonas PS, et al. Aspirin as a therapeutic agent in cardiovascular disease. Circulation 1993;87: 659–675.
29. American Heart Association. Physicians' Health Study report on aspirin. Circulation 1988;77:1447A.
30. Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa: Canada Communication Group, 1994:680–691.
31. American Academy of Family Physicians. Age charts for periodic health examination. Kansas City, MO: American Academy of Family Physicians, 1994. (Reprint no. 510.)
32. Shapiro S. The Physicians' Health Study: aspirin for the primary prevention of myocardial infarction [letter]. N Engl J Med 1988;318:924.