CHEMOPROPHYLAXIS AND IMMUNIZATIONS

Prevention of Cardiovascular Disease:

Risks and Benefits of Aspirin

JULIE E. BURING, ScD, CHARLES H. HENNEKENS, MD, DrPH

Aspirin has been tested for its benefit in preventing cardiovascular disease in randomized trials in three categories of patients. In secondary prevention among those with a history of myocardial infarction (MI), stroke or transient cerebral ischemia, or unstable angina pectoris, 25 randomized trials demonstrated significant reductions from aspirin of 25% for the occurrence of an "important vascular event" (nonfatal MI, nonfatal stroke, or vascular death), 32% for nonfatal MI, 27% for nonfatal stroke, and 15% for vascular mortality. Among those evolving an MI, the Second International Study of Infarct Survival (ISIS-2) showed a significant reduction of 23% in five-week vascular mortality among those started on a one-month regimen of daily aspirin within 24 hours of the onset of symptoms of suspected MI. Aspirin also significantly reduced reinfarction, nonfatal stroke, and important vascular events. Finally, in primary prevention, the US Physicians' Health Study (PHS) showed a significant 44% reduction in the occurrence of a first MI among apparently healthy male physicians; numbers of strokes and vascular deaths were insufficient to permit conclusions for these endpoints. Thus, aspirin is of clear benefit in reducing MI, stroke, and vascular death in secondary prevention and among those evolving an MI. It is also beneficial in the primary prevention of MI among men over 40, but data concerning its effects on stroke and vascular death remain inconclusive.
Key words: *aspirin; cardiovascular disease; prevention; myocardial infarction.* J GEN INTERN MED 1990; 5(suppl):S54–S57.

THE POTENTIAL of low-dose aspirin to reduce risks of cardiovascular disease is derived from basic research, observational analytic studies, and randomized trials. In platelets, small amounts of aspirin irreversibly acetylate the active site of cyclooxygenase, which is required for the production of thromboxane A_2, a powerful promoter of aggregation.[1]

Observational cohort and case–control studies[2, 3] indicate that aspirin may have the potential to reduce risks of cardiovascular disease by about 20%. However, since the size of uncontrolled confounding in observational designs is about as large as the magnitude of the small to moderate effects being sought, the only reliable study design for detecting such small to moderate effects is the randomized trial.[4]

Data from randomized trials of aspirin in three categories of individuals are now available. They include: 1) survivors of myocardial infarction (MI), stroke, or unstable angina pectoris; 2) those evolving an MI; and 3) apparently healthy individuals.

SURVIVORS OF PREVIOUS CARDIOVASCULAR EVENTS

The Anti-Platelet Trialists (APT), representing the investigators worldwide involved in randomized trials of antiplatelet therapy among individuals with a history of cardiovascular disease, have collaborated in a comprehensive overview, or meta-analysis, of all completed trials involving aspirin or two other antiplatelet agents, dipyridamole and sulfinpyrazone.[5] A total of 25 completed randomized trials of aspirin, dipyridamole, or sulfinpyrazone, either alone or in combination, were identified. The study populations for these trials included nearly 29,000 individuals with a history of myocardial infarction, stroke, transient ischemic attack, or unstable angina.

While the results of virtually all these trials were in the direction of a benefit for low-dose aspirin, most were too small in sample size individually to achieve statistical significance. The overview, however, found a statistically significant 25% reduction in risk of developing what was termed an "important vascular event," a category that combined nonfatal MI, nonfatal stroke, and vascular death. For nonfatal MI, when all available trials were considered, there was a statistically significant 32% reduction in risk, while for nonfatal stroke, there was a statistically significant 27% reduction in risk. Finally, with respect to total vascular mortality, there was a statistically significant 15% reduction. When the trials were grouped according to patient-entry criteria, there were significant reductions for each endpoint among the three categories of trials (MI, cerebrovascular, and unstable angina), with the exception of the trials among unstable angina patients, in which there were too few subsequent strokes to allow for reliable estimates of the effect of aspirin on this endpoint.

Received from the Departments of Medicine and Preventive Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts.

Presented at the conference, Frontiers in Disease Prevention, Johns Hopkins University, June 5–6, 1989.

Address correspondence and reprint requests to Dr. Buring: 55 Pond Avenue, Brookline, MA 02146.

The overview also demonstrated that aspirin, the safest, least expensive, and most convenient type of antiplatelet therapy, is at least as effective as dipyridamole or sulfinpyrazone. Moreover, a lower daily dose, 325 mg, or one standard tablet, is no less effective in reducing risks than higher doses of 1 to 1.5 grams daily. In fact, pharmacologic studies suggest that the optimal dosage may be even lower than 80 mg, which is roughly the equivalent of taking one tablet of baby aspirin. The importance of this finding is underscored by the results from the recently completed UK-TIA trial.[6] Since two dosage levels of aspirin as well as placebo were tested in this randomized, double-blind, placebo-controlled trial, the investigators were able to assess whether reported GI side effects were dose-related. For each side effect, the percentage reporting it in the group receiving 300 mg of aspirin daily was higher than the percentage in the placebo group but lower than that in the group receiving 1,200 mg of aspirin daily. Moreover, for symptoms of GI distress, including indigestion, nausea, and heartburn, as well as for GI bleed, the differences between the low- and high-dose groups achieved statistical significance.

Because aspirin appears to confer a moderate degree of protection against the development of cardiovascular endpoints among individuals with a previous history of stroke, MI, or angina, it seemed reasonable to hypothesize a similar benefit if this agent were given during the first several hours following the onset of symptoms of MI.

PATIENTS EVOLVING MYOCARDIAL INFARCTION

To test the hypothesis that low-dose aspirin decreases risks in patients with evolving MI, as well as to assess the role of intravenous streptokinase in treating acute MI, a 2 × 2 factorial design was utilized to conduct ISIS-2, the Second International Study of Infarct Survival.[7] Due to the outstanding efforts of collaborators from more than 400 hospitals in 16 different countries, 17,187 patients were randomized to taking either 160 mg of aspirin or placebo daily for 30 days, beginning immediately upon hospital admission for evolving MI. Patients were also randomized to receiving a single dose of either 1.5 million units of streptokinase or placebo intravenously over 60 minutes. As regards the aspirin findings, the data on mortality five weeks after randomization indicated a statistically significant 23% reduction among those assigned to this agent. For the combined endpoint of all important vascular events, those receiving aspirin had a significant reduction of 28%.

As regards other vascular events during hospitalization, there were no differences between the aspirin and placebo groups for major bleeds or cardiac ruptures. However, for cardiac arrest, those on aspirin experienced significantly fewer events. With respect to reinfarction, there were 156 events in the aspirin group compared with 284 among those on placebo. This reduction was highly statistically significant. And, finally, for stroke, 47 events were experienced in the aspirin group compared with 81 on placebo, a reduction that was also statistically significant.

APPARENTLY HEALTHY INDIVIDUALS

The third category of patients in whom trials of aspirin have been conducted is apparently healthy individuals at usual risk for cardiovascular disease. Two primary prevention trials of aspirin have been carried out, one among 22,071 male U.S. physicians[8] and the other among 5,139 male British physicians.[9]

In December 1987, after an average follow-up of approximately five years, the Data Monitoring Board in the U.S. trial took the unusual step of recommending that the randomized aspirin component of the trial be terminated early. The principal basis for this recommendation was the observation of a highly statistically significant 47% reduction in risk of total MI, which reflected significant benefits of aspirin in reducing both nonfatal and fatal events. The final report from the trial,[10] which considered additional events not confirmed at the time of the preliminary report, indicates a 44% reduction in MI. For total stroke, the relative risk among those receiving aspirin was 1.21, but this finding was not significant ($p = 0.15$). When strokes were subdivided by whether the event was ischemic or hemorrhagic, there was an apparent increase in hemorrhagic stroke that was of borderline statistical significance ($RR = 2.14$, $p = 0.06$). For the combined endpoint of nonfatal MI, nonfatal stroke, and cardiovascular death, there was a highly significant 18% reduction in risk among those allocated to the aspirin group. As regards cardiovascular mortality, there was no difference, but too few cardiovascular deaths were reported to permit an informative test of this hypothesis. The U.K. trial did not show a reduction in MI, stroke, or total vascular mortality, though the 95% confidence intervals were wide. An overview was conducted that considered the preliminary report from the U.S. study and the final report of the British trial. Because the U.S. study was so much larger, the overview demonstrated an overall 33% reduction in nonfatal MI, which was highly statistically significant.[11] These analyses were repeated using data from the final aspirin report of the U.S. trial and yielded a virtually identical 32% reduction in nonfatal MI.

With respect to subgroups of participants in the U.S. trial, analyses indicate that there are no significant modifications of the effects of aspirin across various strata of individuals with the differing risk factors of cigarette smoking, systolic and diastolic blood pressure elevations, levels of physical exercise, diabetes, parental history of MI, alcohol use, and body mass index. However, aspirin's effect on MI risk was modified by

two variables — age and blood cholesterol level. As regards age, the reduction in MI risk associated with aspirin was apparent only among those 50 years of age or older. This may reflect a true effect of aspirin that is present only in those aged 50 or older, or it may simply result from the fact that there were very few MIs among doctors 40–49 years old in the trial, and the absolute risks in the age range are very low. For cholesterol, there was a benefit of aspirin at all levels, but this was even greater for those with lower levels.

As regards gastrointestinal discomfort in the U.S. trial, this was reported by 26.1% of the aspirin group and 25.6% of the placebo group, leaving only 0.5% of such symptoms attributable to aspirin. This very low rate of GI discomfort from an alternate-day dose of 325 mg is consistent with the findings of the UK-TIA[6] and ISIS-2[7] investigations, which indicate that the side effects from aspirin are strongly dose-dependent. A buffered aspirin preparation, as was used in the US trial, may help to minimize GI symptoms, as might the use of an enteric-coated aspirin formulation.

CURRENT KNOWLEDGE OF THE EFFECTS OF ASPIRIN ON CARDIOVASCULAR DISEASE

In secondary prevention among patients with previous MI, stroke, or unstable angina, aspirin definitely reduces the incidences of subsequent MI, stroke, and cardiovascular death, and in 1985 the US Food and Drug Administration approved the prescription labeling of aspirin for the treatment of patients with a previous MI or unstable angina. Similarly, for the treatment of suspected evolving MI, a conclusive benefit is seen for all three cardiovascular endpoints. As regards primary prevention, there is a conclusive reduction in risk of a first MI. This view is supported by the recent report of the U.S. Preventive Services Task Force, which states, "Low-dose aspirin therapy should be considered for men aged 40 and over who are at significantly increased risk for myocardial infarction and who lack contraindications to the drug."[12] As regards aspirin's primary prevention role in stroke and vascular mortality, this remains uncertain due to inadequate numbers of endpoints in the U.S. and British doctors' trials. This should, however, not divert attention from aspirin's firmly established value in secondary prevention.

While aspirin's benefits in secondary prevention and among those evolving an infarction have been demonstrated for both men and women, there are no primary prevention data on aspirin in women. While it may be reasonable to assume that there is a primary preventive effect of aspirin for some categories of women, it is uncertain whether the magnitude of such benefits would be the same in women as in men, or whether the net benefits might be different in some subgroups of women. For example, since coronary risks in women under 60 are much lower than those in men under 60, the risk-to-benefit ratio for such women might be less favorable than that for a similarly aged group of men. These uncertainties underscore the need for a randomized trial of aspirin in healthy women in order to provide definitive data on this question.

The widespread use of nonsteroidal antiinflammatory drugs (NSAIDs), which have antiplatelet properties, has prompted the question of whether patients taking such agents for various indications are also receiving antiplatelet effects commensurate with those of aspirin. While such agents have been demonstrated to inhibit platelet aggregation, this effect appears to be restricted to the time the drug is actually present in bloodstream. Aspirin, on the other hand, inhibits aggregation for the life of the platelet.

It is important to view the results concerning aspirin in the context of what we already know about modification of risk factors to decrease risks of cardiovascular disease. Specifically, as regards blood cholesterol, a 10% decrease corresponds to roughly a 20% decrease in incidence of coronary heart disease.[13] For blood pressure, a 6-mm Hg decrease in diastolic pressure among those with hypertension results in about a 10% lower risk of coronary heart disease, as well as a reduction in risk of approximately 40% for stroke.[14, 15] Finally, in middle age, cessation of cigarette smoking yields about a 37% decrease in risk of coronary heart disease even within a matter of months.[16]

While the presence of cardiovascular risk factors may generally weigh in favor of a decision to prescribe prophylactic aspirin, caution must be exercised in assessing which patients may benefit from aspirin. For example, while a middle-aged man with elevated cholesterol may be a suitable candidate for prophylactic aspirin, the use of aspirin might be contraindicated in a woman in her forties with uncontrolled hypertension, who is at relatively low risk of MI but perhaps at higher risk for hemorrhagic stroke. Thus, aspirin should be viewed as a possible adjunct, not an alternative, to comprehensive risk factor management, which should be prescribed only by a physician or other primary health care provider.[17] The clinical decision for the individual patient should include consideration of that patient's specific cardiovascular risk profile, the known side effects of the drug, and the demonstrated benefits of aspirin in different categories of patients.

REFERENCES

1. Moncada S, Vane JR. Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. N Engl J Med. 1979;300:1142-7.
2. Hennekens CH, Karlson LA, Rosner B. A case–control study of regular aspirin use and coronary deaths. Circulation. 1978; 58:35-8.
3. Hammond EC, Garfinkel L. Aspirin and coronary heart disease: findings of a prospective study. Br Med J. 1975;2:269.
4. Hennekens CH, Buring JE. Epidemiology in medicine. Boston: Little, Brown, 1987.
5. Anti-Platelet Trialists Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet therapy. Br Med J. 1988;296:320-31.

6. UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial interim results. Br Med J. 1988; 296:316-20.
7. 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;II:349-59.
8. 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;318:262-4.
9. Peto R, Gray R, Collins R, et al. A randomised trial of the effects of prophylactic daily aspirin among male British doctors. Br Med J. 1988;296:313-6.
10. 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;321:129-35.
11. Hennekens CH, Peto R, Hutchison GB, Doll R. An overview of the British and American aspirin studies. N Engl J Med. 1988; 318:923-4.
12. Report of the U.S. Preventive Services Task Force. Clinical Guide to Preventive Services. US Department of Health and Human Services, 1989.
13. Peto R, Yusuf S, Collins R. Cholesterol-lowering trial results in their epidemiologic context. Circulation. 1985;72(suppl III):451.
14. Hebert PR, Fiebach NH, Eberlein KA, Taylor JO, Hennekens CH. The community-based randomized trials of pharmacologic treatment of mild-to-moderate hypertension. Am J Epidemiol. 1988;127:581-90.
15. Collins R, Peto R, MacMahon S, et al. Effects of drug treatment for hypertension on the risks of stroke and of coronary heart disease: evidence from an overview of randomised controlled trials considered in the context of observational epidemiology. Lancet. 1990;335:827-38.
16. Hennekens CH, Buring JE, Mayrent S. Smoking, aging and coronary heart disease. In: Bosse R, ed. Smoking and aging. Lexington, MA: D. C. Heath, 1984.
17. Hennekens CH, Buring JE, Sandercook P, Collins R, Peto R. Aspirin in the secondary and primary prevention of cardiovascular diseases. Circulation. 1989;80:749-56.

Adult Immunizations:

Are They Worth the Trouble?

F. MARC LaFORCE, MD

There are good data to recommend routine use of vaccines against measles, rubella, tetanus, influenza, and pneumococcal infections in adults. An adolescent or an adult born after 1956 is considered to be susceptible to measles unless he or she has received two doses of live measles vaccine or has suffered a physician-diagnosed case of measles. Tetanus is largely a disease of the elderly, and there is a universal need for immunizations with tetanus toxoid. Influenza continues to be a major public health problem, and influenza vaccine should be given annually to the elderly and to those at high risk. The efficacy of pneumococcal vaccine in American adults is still being debated. Results from case-control studies show that the vaccine is about 60% effective in reducing the incidence of disease due to vaccine-related strains. Its use in the elderly and in those at higher risk for pneumococcal infection is recommended. **Key words:** ***immunizations; elderly; pneumococcal vaccine; influenza vaccine; health promotion; adult health care.*** **J GEN INTERN MED 1990; 5(suppl):S57-S61.**

VACCINES ARE ONE of the most cost-effective approaches to improved health care. Childhood vaccinations have increased life expectancy among Americans more than have all investments in tertiary care, and at a fraction of the cost. The incidences of measles encephalitis and the congenital rubella syndrome are at an all-time low. Interest in adult immunizations has increased over the last decade with specific efforts to improve vaccination coverage of adults from the American College of Physicians, the Division of Immunization at the Centers for Disease Control (CDC), and the U.S. Preventive Services Task Force. Despite this renewed interest, significant gaps in vaccine coverage of adult Americans remain.

TABLE 1

Routine Adult Immunization Recommendations Based on Age

Vaccine	Age		
	18-24 Years	25-64 Years	65 Years or Older
Measles	x	x*	
Rubella	x	x*	
Influenza			x
Pneumococcal			x

*For susceptible patients.

Table 1 lists the routinely recommended vaccinations for adults by age. This paper reviews the rationale and the evidence in favor of their use. Pneumococcal vaccine is discussed in more detail because of the controversy surrounding its use. Readers are referred to more comprehensive publications from the CDC Immunization Division,[1] recommendations from the Advisory Committee on Immunization Practices, which are published regularly in *MMWR* and the textbook *Vaccines,* edited by Plotkin and Mortimer.[2] The U.S. Preventive Services Task Force format, which includes burden of suffering, the vaccine, and evidence for efficacy, is used to discuss each vaccine.

Received from the Department of Medicine, The Genesee Hospital and the University of Rochester School of Medicine and Dentistry, Rochester, New York.

Presented at the conference, Frontiers in Disease Prevention, The Johns Hopkins University, June 5-6, 1989.

Address correspondence and reprint requests to Dr. LaForce: The Genesee Hospital, 224 Alexander Street, Rochester, NY 14607.