Clinical Practice

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

Aspirin for Primary Prevention of Coronary Events

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A 45-year-old man with a strong family history of premature heart disease has no symptoms of coronary disease and has a normal electrocardiogram. A fasting lipid analysis reveals a total cholesterol level of 225 mg per deciliter (5.8 mmol per liter), a high-density lipoprotein cholesterol level of 35 mg per deciliter (0.9 mmol per liter), a triglyceride level of 150 mg per deciliter (1.7 mmol per liter), and a low-density lipoprotein cholesterol level of 160 mg per deciliter (4.1 mmol per liter). The man's resting systolic blood pressure is 125 mm Hg, and he has never taken any medications for hypertension. He is a nonsmoker and is physically active. Should he be advised to take aspirin to reduce his risk of coronary events?

The Clinical Problem

The primary prevention of coronary heart disease involves the deliberate treatment of persons with established risk factors in order to prevent coronary events in those without manifest clinical disease.[1] Approximately 25 percent of the reduction in the rate of death from coronary disease that has occurred during the past 30 years may be explained by the practice of primary prevention.[2] In addition to the established risk factors of hypertension, smoking, hypercholesterolemia, and sedentary lifestyle, all of which have been identified as targets for primary prevention,[1] the risk of clinical coronary disease is known to be related to platelet activity[3] and inflammation.[4,5] Because aspirin has both antiplatelet[6] and antiinflammatory[5] effects, it has been proposed and tested for use in primary prevention.[7,8]

Risk reduction is a decrease in the relative risk or the absolute risk of an event.[9] The relative risk is a calculation of the ratio of the absolute rates of events in two different groups and is used in clinical research to assess the magnitude of an association. Knowledge of the absolute risk is important in considering the appropriate treatment for individual patients. Recently described algorithms from the Framingham Heart Study facilitate the assessment of the absolute risk of coronary events in individual patients (Fig. 1).[11,12] This scoring system has some limitations, including its reliance on lipid levels measured before drug treatment and the lack of confidence intervals around risk estimates. Nonetheless, it provides useful estimates of a patient's absolute risk that are critical to decisions about whether to institute a strategy of primary prevention such as aspirin therapy.

Strategies and Evidence

Observational Studies

In the 1970s, prospective cohort and case–control studies suggested that regular aspirin use could reduce the risk of myocardial infarction and death from coronary causes.[13-15] Two large observational studies have been published recently. A report from the Nurses' Health Study analyzed the rates of coronary events among 87,678 women who were followed for six years.[16] Among all women, regular intake of one to six aspirin tablets per week was associated with a reduction in the combined rate of nonfatal myocardial infarction and fatal coronary heart disease (multivariable-adjusted relative risk, 0.75; 95 percent confidence interval, 0.58 to 0.99). Among women younger than 50 years of age, there was no benefit associated with aspirin use (age-standardized rates of events among aspirin users and nonusers, 22 and 23 per 100,000 person-years, respectively). In contrast, among women 50 to 54 years of age, aspirin use was associated with lower rates of coronary events (62 vs. 121 per 100,000 person-years), as it was among women 55 years of age or older (112 vs. 165 per 100,000 person-years). There was no association between aspirin use and stroke, and there was a nonsignificant trend toward a reduced rate of death from any cause.

In another observational study involving 6174 patients at the Cleveland Clinic Foundation who had known or suspected coronary disease and who were referred for stress echocardiography, aspirin use was

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associated with a reduced risk of death from any cause (multivariable-adjusted relative risk, 0.67; 95 percent confidence interval, 0.51 to 0.87).[17] In a subgroup analysis that took into account the likelihood that a patient would use aspirin, aspirin use was associated with reduced mortality among patients without coronary disease only if they had impaired functional capacity and were at least 60 years old (mortality, 5 percent vs. 8 percent during three years of follow-up). The authors hypothesized a priori that aspirin use might be particularly beneficial in physically unfit patients, given the known correlations between poor fitness and platelet hyperreactivity.[18]

Randomized Trials

There have been five major randomized trials of aspirin for the primary prevention of coronary events: the British Doctors' Trial,[19] the Physicians' Health Study[7] in the United States, the Thrombosis Prevention Trial,[20] the Hypertension Optimal Treatment Study,[21] and the Primary Prevention Project.[22] With the exception of the British Doctors' Trial, all showed a reduction in the rates of cardiovascular events that was driven primarily by a reduction in the occurrence of myocardial infarction.[8] The reductions in the relative risk of myocardial infarction ranged from 4 percent to 44 percent; the reductions in the absolute risk ranged from 0.03 percent per year to 0.31 percent per year; and the number of patients who would need to be treated to prevent one myocardial infarction during five years of treatment ranged from 65 to 667. None of the trials showed a reduction in the risk of death from any cause or in the risk of stroke, but none were statistically powered for such analyses.

With the exception of the British Doctors' Trial, all the trials showed an increase in the risk of clinical hemorrhage with aspirin use.[8] In general, the most common site of major bleeding (bleeding leading to death, transfusion, or surgery) was the gastrointestinal tract; common types of minor bleeding were epistaxis and easy bruising.[7,20-22] A meta-analysis of 16 placebo-controlled trials of aspirin for cardiac and other indications found that aspirin increased the absolute risk of cerebral hemorrhage by 12 events per 30,000 person-years of follow-up (95 percent confidence interval, 5 to 20).[23]

A recently published meta-analysis[8] of four of the primary-prevention trials (the Primary Prevention Project[22] was not included because its results were published later) found that aspirin use led to a reduction in the risk of cardiovascular events (relative risk, 0.85; 95 percent confidence interval, 0.78 to 0.94) but was also associated with an increased risk of major noncerebral bleeding episodes (absolute annual risk with and without aspirin, 0.09 percent and 0.05 percent, respectively; relative risk, 1.69; 95 percent confidence interval, 1.38 to 2.07). Furthermore, the potential benefit of aspirin appeared to be highly dependent on the absolute risk of myocardial infarction at base line. When the base-line risk of myocardial infarction is only 0.5 percent per year, the reduction in the absolute risk with aspirin use, when likely episodes of major bleeding are taken into account, is only 0.08 percent per year (Table 1). In contrast, among patients with a base-line risk of 1.5 percent per year, aspirin use reduces the absolute risk by 0.4 percent per year.

A recent meta-analysis that included the Primary Prevention Project as well as other systematic reviews and observational studies yielded similar results.[24] When the five-year absolute risk of coronary events reached 5 percent, aspirin treatment reduced the absolute risk of coronary events by 0.3 percent per year but increased the risk of hemorrhagic stroke by 0.02 percent per year and the risk of major gastrointestinal bleeding by 0.06 percent per year. In contrast, when the five-year absolute risk of coronary events was only 1 percent, aspirin treatment resulted in a reduction of only 0.06 percent per year in the absolute risk.

AREAS OF UNCERTAINTY

Aspirin Dose

In the five primary-prevention trials, the doses of aspirin used varied from 75 mg once a day to 500 mg once a day. There has been no primary-prevention trial to date that has compared different doses of aspirin. Studies of aspirin dosage and platelet function have suggested that, for the prevention of myocardial infarction, low doses of aspirin (100 mg per day or less) are adequate.[25] Furthermore, for other clinical purposes, such as the prevention of stroke, low-dose aspirin is just as effective as high-dose therapy.[26] It is also unclear whether the risk of major bleeding is associated with the dose of aspirin.[27]

Benefits in Specific Subgroups

Most participants in the randomized trials of aspirin were men. Thus, it is unclear whether aspirin therapy prevents myocardial infarction in women, although observational data from the very large Nurses' Health Study cohort[17] suggest that it may. An ongoing study of 40,000 female health care professionals in the United States is comparing low-dose aspirin (100 mg orally every other day) with placebo for the primary prevention of coronary disease.[28]

Although one of the trials of aspirin for the prevention of coronary disease specifically focused on patients with hypertension,[21] concern has been expressed that aspirin may be less beneficial,[7] or perhaps even dangerous, in patients with high blood pressure. According to a post hoc subgroup analysis[29] in the Thrombosis Prevention Trial,[20] aspirin led to a significant reduc-

tion in the rate of coronary events among patients with base-line systolic blood pressure of less than 130 mm Hg (relative risk as compared with patients who did not receive aspirin, 0.55), but not among those with a base-line systolic blood pressure of more than 145 mm Hg (relative risk, 0.94). Although this subgroup analysis must be interpreted cautiously, it suggests that adequate blood-pressure control is particularly critical among patients for whom aspirin is prescribed for the prevention of coronary disease.[29]

Diabetes mellitus is associated with a risk of fatal coronary heart disease that is as high as the risk associated with a history of myocardial infarction in patients without diabetes.[30] Whether prophylactic aspirin therapy reduces the risk of coronary events in patients with diabetes has not been systematically studied. In the Physicians' Health Study, aspirin use reduced the risk of myocardial infarction in patients with diabetes from 10 percent to 4 percent during five years of follow-up, and no interactions with treatments for diabetes were noted.[7] In the Early Treatment Diabetic Retinopathy Study, a randomized trial involving 3711 patients with diabetes and nonproliferative or early proliferative retinopathy, myocardial infarction tended to be less frequent among subjects randomly assigned to receive 650 mg of aspirin per day than among those assigned to placebo[31]; aspirin had no effect on the progression of eye disease.[32]

In addition to inhibiting thrombosis, aspirin is an antiinflammatory drug. According to a subgroup analysis in the Physicians' Health Study, the benefit of aspirin was largely confined to men who had elevated levels of C-reactive protein.[5] Further study is needed to determine whether measurement of the level of C-reactive protein would be a better means of identifying appropriate candidates for aspirin therapy than currently used measures, such as the Framingham risk score.[33]

Aspirin inhibits the activity of cyclooxgenase-1, thereby inhibiting the synthesis of vasodilatory prostaglandins. In contrast, angiotensin-converting–enzyme (ACE) inhibitors inhibit the breakdown of bradykinin, leading to an increase in the production of these prostaglandins.[34] Because of these opposing effects, there is concern that aspirin may adversely affect beneficial hemodynamic effects of ACE inhibitors — a phenomenon that has been observed in a randomized trial.[35] Observational analyses of patients enrolled in trials of treatments for coronary heart disease or congestive heart failure have suggested that the benefits of aspirin and ACE inhibitors may be attenuated when both agents are used together,[36-38] but a recent meta-analysis of data on patients who had had myocardial infarctions showed no such interaction.[39] Whether or not this interaction, if it exists, affects the efficacy of aspirin in primary prevention is unknown.

Other Benefits

Several observational studies have suggested that aspirin may prevent cancer of the colon, esophagus, stomach, and rectum,[40,41] but this has not yet been shown in randomized trials. In a cohort study involving 653,031 adults enrolled in the Cancer Prevention Study II, intake of at least 16 aspirin tablets per month was associated with a risk of gastrointestinal cancer that was 34 to 47 percent lower than that found among nonusers of aspirin, even after confounding factors had been accounted for.[41] The absolute risk of colon cancer was reduced from 0.20 percent to 0.12 percent over a period of five years. It is possible that aspirin must be used regularly for a long time in order for the benefit to emerge,[40] as has been suggested by studies in animals.[42]

Aspirin Resistance

Approximately 5 to 10 percent of patients with stable coronary disease do not have a decrease in platelet function when they are given aspirin; these patients with aspirin resistance tend to be older and are more often women and nonsmokers.[43] It is not known whether aspirin resistance predicts a worse overall prognosis or a lack of clinical benefit from aspirin therapy.

Dual Antiplatelet Therapy

Two recent trials showed that patients with acute coronary syndromes and patients undergoing percutaneous coronary interventions may have lower rates of coronary events if they are treated with both clopidogrel and aspirin than if they are treated with aspirin alone.[44,45] Whether or not such combination therapy might provide additional benefit in patients with aspirin resistance or other high-risk patients without clinically manifest coronary disease will be tested in future randomized trials.[46]

GUIDELINES

The U.S. Preventive Services Task Force recently noted that there was good evidence that aspirin decreases the risk of coronary heart disease in those who

Figure 1 (facing page). Framingham Scoring System for Calculating the 10-Year Risk of Major Coronary Events in Adults without Diabetes.

HDL denotes high-density lipoprotein cholesterol, and BP blood pressure. All age ranges are given in years. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. Reprinted from the National Heart, Lung, and Blood Institute.[10]

Estimate of 10-Year Risk for Men
(Framingham Point Scores)

Age	Points
20–34	−9
35–39	−4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Total cholesterol (mg/dl)	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
⩾280	11	8	5	3	1

	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dl)	Points
⩾60	−1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	Points	
	If untreated	If treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
⩾160	2	3

	Point total	10-Year risk %
	<0	<1
	0	1
	1	1
	2	1
	3	1
	4	1
	5	2
	6	2
	7	3
	8	4
	9	5
	10	6
	11	8
	12	10
	13	12
	14	16
	15	20
	16	25
10-Year risk_____%	⩾17	⩾30

Estimate of 10-Year Risk for Women
(Framingham Point Scores)

Age	Points
20–34	−7
35–39	−3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Total cholesterol (mg/dl)	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
⩾280	13	10	7	4	2

	Points				
	Age: 20–39	40–49	50–59	60–69	70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dl)	Points
⩾60	−1
50–59	0
40–49	1
<40	2

Systolic BP (mm Hg)	Points	
	If untreated	If treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
⩾160	4	6

	Point total	10-Year risk %
	<9	<1
	9	1
	10	1
	11	1
	12	1
	13	2
	14	2
	15	3
	16	4
	17	5
	18	6
	19	8
	20	11
	21	14
	22	17
	23	22
	24	27
10-Year risk_____%	⩾25	⩾30

TABLE 1. EFFECT OF BASE-LINE RISK ON THE NUMBER OF PATIENTS WHO WOULD NEED TO BE TREATED WITH ASPIRIN IN ORDER TO PREVENT ONE MYOCARDIAL INFARCTION OVER A PERIOD OF FIVE YEARS.*

BASE-LINE RISK OF MYOCARDIAL INFARCTION	NUMBER NEEDED TO TREAT FOR 5 YR	
	TO PREVENT 1 MYOCARDIAL INFARCTION	TO PREVENT 1 MYOCARDIAL INFARCTION WITHOUT A MAJOR BLEEDING EPISODE†
0.5%/yr	133	256
1.0%/yr	67	88
1.5%/yr	44	53

*Data were adapted from Sanmuganathan et al.[8] It is assumed that the reduction in relative risk with aspirin is 30 percent and that the risk of bleeding is independent of the base-line risk of myocardial infarction.

†Major bleeding episodes include cerebral hemorrhage or a bleeding episode leading to death or necessitating transfusion or surgery. The number needed to treat is higher when episodes of major bleeding are taken into account because such episodes diminish the net benefit of aspirin.

are at increased risk for this condition but added that there is also good evidence that it increases the risk of gastrointestinal bleeding and fair evidence that it increases the risk of hemorrhagic stroke. Overall, the task force supported the use of aspirin for the primary prevention of coronary disease in patients whose five-year risk of disease was estimated to be 3 percent or higher, but it acknowledged that the preferences of the patient should also be factored into decisions about aspirin use.[47] The "Guide to Primary Prevention of Cardiovascular Diseases" published by the American Heart Association in 1997 did not even mention aspirin as a preventive strategy.[1] A 1997 Statement for Healthcare Professionals by the American Heart Association did not recommend the use of aspirin for primary prevention, but it stated that "aspirin therapy may be warranted in patients at risk for myocardial infarction. However, such use must at present be based on an individual clinical judgment by providers that takes into account a patient's particular cardiovascular risk profile."[48]

Recent guidelines from the Second Joint Task Force of European and Other Societies on Coronary Prevention emphasize the importance of estimating absolute coronary risk for designing primary-preven-

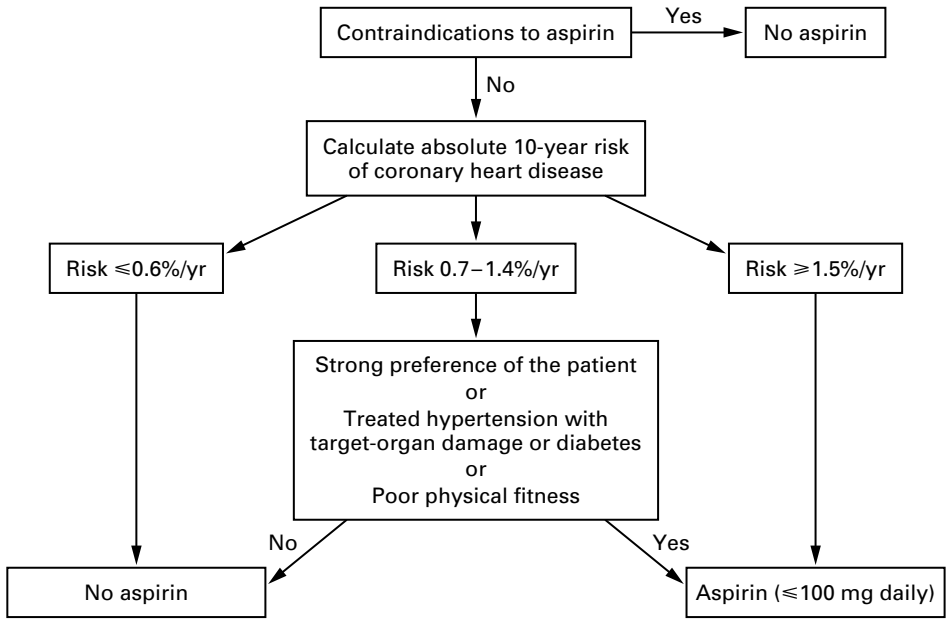

Figure 2. Suggested Algorithm for Making Decisions about the Use of Aspirin for Primary Prevention of Coronary Heart Disease.

Contraindications to aspirin therapy include known allergy, bleeding diathesis, platelet disorders, and active peptic ulcer disease. Relative contraindications include renal failure, concurrent use of nonsteroidal antiinflammatory agents or anticoagulants, and uncontrolled hypertension. The risk of coronary heart disease is estimated with the use of the Framingham risk score. Poor physical fitness is defined as impaired exercise capacity for age and sex.[17]

tion regimens.[49] These guidelines recommend 75 mg of aspirin daily in patients with treated hypertension and in men who are at particularly high risk for coronary heart disease.[49] Finally, 1999 guidelines for the management of hypertension from the British Hypertension Society recommend aspirin therapy for primary prevention in hypertensive patients 50 years of age or older who have satisfactory control of their blood pressure (<150/90 mm Hg) and either target-organ damage, diabetes, or a 10-year risk of coronary heart disease of at least 15 percent.[50] The recommendation for aspirin use in patients with diabetes is consistent with guidelines for the management of hyperlipidemia that consider diabetes to be as prognostically ominous as coronary heart disease.[33]

CONCLUSIONS AND RECOMMENDATIONS

Aspirin use probably reduces the risk of myocardial infarction in men over the age of 50 years. For individual patients, the decision to initiate aspirin therapy should be based on a careful assessment of absolute risk. The absolute risk of major coronary events should be calculated as the Framingham risk score.[11,12,33] This can easily be done in the physician's office with the use of an on-line or downloaded version of the scoring system (for example, that available at http://www.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof). A suggested algorithm for making decisions about the use of aspirin therapy on the basis of predictions of absolute risk is presented in Figure 2. Patients with an estimated risk of coronary events of 1.5 percent per year or higher are, barring contraindications, good candidates for aspirin therapy, whereas those with a risk of 0.6 percent per year or less are probably not. Among patients with an intermediate level of risk — that is, 0.7 to 1.4 percent per year — other factors should be considered, including the preferences of the patient; treatment should be considered more seriously if there is adequately treated hypertension with target-organ damage, diabetes mellitus,[50] or poor physical fitness.[10]

For the patient in the case vignette, the risk of myocardial infarction may initially appear high relative to that of others with a more favorable lipid profile and family history, yet the calculated absolute risk is only 0.6 percent per year.[33] Given his low absolute risk and the absence of other factors such as hypertension, diabetes, and poor physical fitness, I would recommend against the use of aspirin. I would explain that in his case, the absolute benefit of aspirin use would be low, whereas he would have a small but real risk of major bleeding. Nonetheless, his absolute risk should be reassessed at least once every three to five years, since it might well increase to a point at which aspirin therapy would be appropriate.

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