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FINAL REPORT ON THE ASPIRIN COMPONENT OF THE ONGOING PHYSICIANS' HEALTH STUDY

STEERING COMMITTEE OF THE PHYSICIANS' HEALTH STUDY RESEARCH GROUP*

Abstract The Physicians' Health Study is a randomized, double-blind, placebo-controlled trial designed to determine whether low-dose aspirin (325 mg every other day) decreases cardiovascular mortality and whether beta carotene reduces the incidence of cancer. The aspirin component was terminated earlier than scheduled, and the preliminary findings were published. We now present detailed analyses of the cardiovascular component for 22,071 participants, at an average follow-up time of 60.2 months.

There was a 44 percent reduction in the risk of myocardial infarction (relative risk, 0.56; 95 percent confidence interval, 0.45 to 0.70; P<0.00001) in the aspirin group (254.8 per 100,000 per year as compared with 439.7 in the placebo group). A slightly increased risk of stroke among those taking aspirin was not statistically significant; this trend was observed primarily in the subgroup with hemorrhagic stroke (relative risk, 2.14; 95 percent confidence interval, 0.96 to 4.77; P = 0.06). No reduction in mortality from all cardiovascular causes was associated with aspirin (relative risk, 0.96; 95 percent confidence interval, 0.60 to 1.54).

Further analyses showed that the reduction in the risk of myocardial infarction was apparent only among those who were 50 years of age and older. The benefit was present at all levels of cholesterol, but appeared greatest at low levels. The relative risk of ulcer in the aspirin group was 1.22 (169 in the aspirin group as compared with 138 in the placebo group; 95 percent confidence interval, 0.98 to 1.53; P = 0.08), and the relative risk of requiring a blood transfusion was 1.71.

This trial of aspirin for the primary prevention of cardiovascular disease demonstrates a conclusive reduction in the risk of myocardial infarction, but the evidence concerning stroke and total cardiovascular deaths remains inconclusive because of the inadequate numbers of physicians with these end points. (N Engl J Med 1989; 321: 129-35.)

ALTHOUGH chewing willow bark, which has aspirin-like properties, was prescribed for pain relief by Hippocrates in the fifth century B.C., the possible role of aspirin in reducing the risk of cardiovascular disease has been recognized only very recently. Such a possibility derives from the capacity of aspirin in low doses to inhibit cyclooxygenase-dependent platelet enzymes virtually completely, resulting in the inhibition of aggregability for the life of the platelet.[1] These effects are so profound that higher doses add little benefit but do increase the risk of side effects.[2] Although an early case–control study[3] raised the possibility of a large benefit, most observational studies[4,5] have suggested a cardiovascular benefit of about 20 percent. In such circumstances, the amount of uncontrolled confounding in case–control or cohort studies may be as large as the small-to-moderate effects being sought[6]; consequently, conclusive data can result only from a randomized trial whose sample is sufficiently large.[7,8]

The Physicians' Health Study is a double-blind, placebo-controlled, randomized trial designed to test two primary-prevention hypotheses in a population of healthy male physicians: whether aspirin in low doses (Bufferin, Bristol-Myers Products, 325 mg every other day) reduces mortality from cardiovascular disease, and whether beta carotene (Lurotin, BASF, 50 mg on alternate days) decreases the incidence of cancer. Although the beta carotene component of the trial is continuing at least through 1990, the Data Monitoring Board recommended the early termination of the

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blinded aspirin component of the trial on December 18, 1987. This decision was based on all available evidence, including three major considerations: the presence of a significant ($P<0.00001$) reduction in the risk of total myocardial infarction among those in the aspirin group; the fact that no effect of aspirin on cardiovascular mortality could be detected in the trial until the year 2000 or later, because of the exceptionally low cardiovascular death rates among the participating physicians; and the fact that aspirin was subsequently prescribed for more than 85 percent of the participants who experienced nonfatal vascular events, which made any finding about cardiovascular mortality particularly difficult to interpret. The trial's preliminary findings were published on January 28, 1988.[9] We report here the results of the final analyses of the cardiovascular component up to January 25, 1988, when the participants were told whether they had been assigned to the aspirin or the placebo group.

Methods

The subjects and methods of the Physicians' Health Study were described in detail in the preliminary report.[9] Briefly, 22,071 physicians were randomly assigned, according to two-by-two factorial design,[10] to one of four treatment groups: aspirin and beta carotene, aspirin and beta carotene placebo, aspirin placebo and beta carotene, or aspirin placebo and beta carotene placebo. Altogether, 11,037 physicians were assigned at random to receive aspirin and 11,034 to receive aspirin placebo. All 22,071 participants randomly assigned to a treatment group have been included in all analyses.

Every six months for the first year and annually thereafter, the participants were sent a supply of monthly calendar packs (provided by Bristol-Myers Products) containing white tablets (aspirin or placebo) for odd-numbered days and red capsules (beta carotene or placebo) for even-numbered days. They were also sent brief questionnaires asking about their compliance with the treatment regimen and the occurrence of any relevant events.

By January 25, 1988, the participants had been followed for an average of 60.2 months (range, 45.8 to 77.0); 99.7 percent were still providing information on morbidity, and the vital status of all 22,071 doctors was known. The reported consumption of aspirin or other platelet-active drugs was 85.71 percent in the aspirin group and 14.23 percent in the placebo group. A total of 1269 physicians (624 taking aspirin and 645 taking aspirin placebo) requested an enteric-coated preparation (supplied by Bristol-Myers Products), and an additional 29 (16 assigned to aspirin and 13 assigned to placebo) specifically requested Ecotrin or its placebo (supplied by SmithKline Beckman).

When a participant reported a relevant outcome event, written consent for the review of his medical records was obtained. The information was requested from hospitals and responsible physicians. Reported diagnoses of cardiovascular disease or deaths were considered confirmed only after the examination of all available information by an End Points Committee of physicians that included two internists, a cardiologist, and a neurologist, all blinded to the assigned treatment. When written consent or the relevant records could not be obtained, a reported event could not be confirmed. Records were available for review for 95.6 percent of the reported myocardial infarctions, 95.2 percent of the strokes, and 94.8 percent of all deaths. All our analyses were based on confirmed events.

The diagnoses of nonfatal myocardial infarction were confirmed with use of the criteria of the World Health Organization.[11] Nonfatal stroke was defined as a typical neurologic deficit that was sudden or rapid in onset, lasted more than 24 hours, and was attributable to a cerebrovascular event. Strokes were further classified according to the severity of the residual impairment at the time of hospital discharge (mild, moderate, or severe) and according to the probable cause (ischemic or hemorrhagic) on the basis of medical records and the judgment of the neurologist. Death due to a cardiovascular cause was documented by convincing evidence of a cardiovascular mechanism from all available sources, including death certificates, hospital records, and — for death outside the hospital — observers' impressions.

For the end points of myocardial infarction and stroke (Tables 1 and 2), only the first event within each category was counted. For cardiovascular mortality (Table 3), all deaths were included in the analyses. Thus, for the 15 subjects who had both a nonfatal myocardial infarction and a nonfatal stroke, both events were counted as end points. For the 23 who had a nonfatal myocardial infarction (or stroke) followed by death from a cardiovascular cause, the nonfatal event was included in our analysis of myocardial infarction (or stroke), and the fatal event was included in cardiovascular deaths. In addition, we performed analyses using as end points only the first cardiovascular event experienced by the participants — myocardial infarction, stroke, or cardiovascular death — and this method yielded virtually identical results. For the combined end point of nonfatal myocardial infarction, nonfatal stroke, and death from a cardiovascular cause, only a participant's first cardiovascular event was counted.

The relative risk was calculated as the number of events per person-year of observation in the aspirin group divided by the corresponding number in the placebo group after adjustment for age and for assignment to beta carotene treatment,[12] even though no significant effect of beta carotene was observed on any of the major cardiovascular end points. Since the trial was so large, the adjusted ratios were, in practice, never materially different from the ratios of the crude numbers affected in each group.[8] For each relative risk, the two-sided P value and the 95 percent confidence interval were calculated.[12] Multiple logistic-regression analysis[12] was used to control simultaneously for the joint effects of any small differences in base-line cardiovascular risk factors, although no individual factor differed significantly between the aspirin and placebo groups.

Results

There were 139 myocardial infarctions among those assigned to aspirin and 239 among those assigned to aspirin placebo (relative risk, 0.56; 95 percent confidence interval, 0.45 to 0.70; $P<0.00001$) (Table 1). This represents a 44 percent reduction in risk, and the benefits of aspirin were significant for both fatal and nonfatal myocardial infarction. In terms of absolute rates of events, the figures can be extrapolated to 254.8 per 100,000 per year in the aspirin group and 439.7 per 100,000 per year in the placebo group. As for total stroke, there were 119 events in the aspirin group and 98 in the placebo group — an increase in risk that was not statistically significant (relative risk, 1.22; 95 percent confidence interval, 0.93 to 1.60; $P = 0.15$). Strokes were then subdivided into ischemic and hemorrhagic events and, further, into those resulting in mild, moderate, or severe disability or death (Table 2). In the subgroup with hemorrhagic strokes, aspirin was associated with an increased risk that was of borderline statistical significance (relative risk, 2.14; 95 percent confidence interval, 0.96 to 4.77; $P = 0.06$). This subgroup included 10 mild hemorrhagic strokes in the aspirin group and 6 in the placebo group (relative risk, 1.67; 95 percent confidence interval, 0.61 to 4.57; $P = 0.32$), as well as 13 moderate-to-severe or fatal hemorrhagic strokes in the aspirin group and 6 in the placebo group (relative risk, 2.19; 95 percent confidence interval, 0.84 to 5.69; $P = 0.11$).

With respect to total cardiovascular mortality (Table 3), there were 81 deaths among those assigned to aspirin and 83 among those given placebo (relative risk, 0.96; 95 percent confidence interval, 0.60 to 1.54;

Table 1. Confirmed Cardiovascular End Points in the Aspirin Component of the Physicians' Health Study, According to Treatment Group.*

End Point	Aspirin Group	Placebo Group	Relative Risk	95% Confidence Interval	P Value
Myocardial infarction					
Fatal	10	26	0.34	0.15–0.75	0.007
Nonfatal	129	213	0.59	0.47–0.74	<0.00001
Total	139	239	0.56	0.45–0.70	<0.00001
Person-years of observation	54,560.0	54,355.7	—	—	—
Stroke					
Fatal	9	6	1.51	0.54–4.28	0.43
Nonfatal	110	92	1.20	0.91–1.59	0.20
Total	119	98	1.22	0.93–1.60	0.15
Person-years of observation	54,650.3	54,635.8	—	—	—

*Additional events that could not be confirmed because records were not available included 17 myocardial infarctions (10 in the aspirin group and 7 in the placebo group) and 11 strokes (3 aspirin and 8 placebo).

P = 0.87). In the five categories of death from specific cardiovascular causes, there was only one statistically significant finding: a reduction in the rate of fatal myocardial infarction (10 in the aspirin group and 28 in the placebo group; P = 0.004). For sudden death, there was an apparent increase in risk that did not achieve statistical significance (22 in the aspirin group and 12 in the placebo group; P = 0.09). Combining the category of fatal acute myocardial infarction (ICD [*International Classification of Diseases* number] 410) with the categories of all other fatal ischemic heart disease (ICD 411 to 414) yielded 34 deaths in the aspirin group and 53 in the placebo group (relative risk, 0.60; 95 percent confidence interval, 0.37 to 0.98; P = 0.04). The addition of sudden death (ICD 798) resulted in 56 deaths in the aspirin group and 65 in the placebo group (relative risk, 0.86; 95 percent confidence interval, 0.60 to 1.22; P = 0.41). There was no reduction in the risk of all deaths from noncardiovascular causes (124 in the aspirin group vs. 133 in the placebo group; relative risk, 0.93; 95 percent confidence interval, 0.72 to 1.20; P = 0.59). Thus, there were 205 deaths with a confirmed cause in the aspirin group and 216 in the placebo group (relative risk, 0.95; 95 percent confidence interval, 0.79 to 1.15; P = 0.60).

To help clarify a risk-to-benefit ratio, we considered a combined end point consisting of nonfatal myocardial infarction, nonfatal stroke, and death from a cardiovascular cause. There were 307 important vascular events among those assigned to aspirin and 370 among those assigned to placebo (relative risk, 0.82; 95 percent confidence interval, 0.70 to 0.96; P = 0.01). This represents a statistically significant, 18 percent reduction in important vascular events among those assigned to aspirin.

As expected with a sample of 22,071 participants randomly assigned to treatment groups, there were no differences in the base-line characteristics — age, cigarette smoking, incidence of diabetes mellitus, parental history of myocardial infarction, cholesterol level, systolic blood pressure, diastolic blood pressure, alcohol use, amount of vigorous exercise, and body-mass index. When the possible effects of any differences in the joint distributions of these risk factors were taken into account through logistic regression, the relative risks for each cardiovascular end point were unchanged.

We also examined the possible effects of aspirin in subgroups of physicians with various cardiovascular risk factors. As shown in Table 4, the effects of aspirin on the risk of myocardial infarction were modified by two coronary risk factors — age and blood cholesterol level. The reduction in the risk of myocardial infarction associated with the use of aspirin was apparent only in those 50 years of age or older (P = 0.02). No consistent effect of age on the relation between aspirin and either stroke or cardiovascular mortality was observed. For cholesterol, the beneficial effects of aspirin on myocardial infarction were apparent at all levels but appeared greatest at low levels (P = 0.04). For cigarette smoking, the reduction in the risk of myocardial infarction associated with the use of aspirin was similar among those who had never smoked, past smokers, and current smokers. For stroke, cigarette smoking did not modify the effect of aspirin, but for cardiovascular mortality, it appeared to do so (P = 0.05). However, neither the observed reduction in risk among nonsmokers (P = 0.18) nor the apparently increased risk among current smokers (P = 0.20) was significant. Finally, blood-pressure levels had no consistent effect on the association between aspirin and myocardial infarction, stroke, or mortality from cardiovascular causes.

During the 60.2 months of follow-up, gastrointestinal discomfort was reported by 26.1 percent of the aspirin group and 25.6 percent of the placebo group; 0.5 percent was therefore attributable to the active drug, a nonsignificant excess (P = 0.45) (Table 5). For all gastrointestinal symptoms except ulcer, the corresponding figures were 34.8 percent and 34.2 percent, respectively (P = 0.48, also not significant).

Table 2. Subcategories of Stroke, According to Treatment Group.*

Type of Stroke	Aspirin Group	Placebo Group	Relative Risk	95% Confidence Interval	P Value
Ischemic					
Mild	69	61	1.13	0.80–1.60	0.48
Moderate, severe, or fatal	21	20	1.05	0.57–1.95	0.88
Unknown severity	1	1			
Total	91	82	1.11	0.82–1.50	0.50
Hemorrhagic					
Mild	10	6	1.67	0.61–4.57	0.32
Moderate, severe, or fatal	13	6	2.19	0.84–5.69	0.11
Total	23	12	2.14	0.96–4.77	0.06
Unknown cause					
Mild	2	1	—	—	—
Moderate, severe, or fatal	1	2	—	—	—
Unknown severity	2	1	—	—	—
Total	5	4	—	—	—
Total	119	98	1.22	0.93–1.60	0.15

*Severity was defined as follows: mild, impairment not affecting functioning; moderate, functional impairment; and severe, a major change in way of life or dependence.

Table 3. Confirmed Deaths, According to Treatment Group.

CAUSE*	ASPIRIN GROUP	PLACEBO GROUP	RELATIVE RISK	95% CONFIDENCE INTERVAL	P VALUE
Total cardiovascular deaths†	81	83	0.96	0.60–1.54	0.87
Acute myocardial infarction (410)	10	28	0.31	0.14–0.68	0.004
Other ischemic heart disease (411–414)	24	25	0.97	0.60–1.55	0.89
Sudden death (798)	22	12	1.96	0.91–4.22	0.09
Stroke (430, 431, 434, 436)‡	10	7	1.44	0.54–3.88	0.47
Other cardiovascular (402, 421, 424, 425, 428, 429, 437, 440, 441)	15	11	1.38	0.62–3.05	0.43
Total noncardiovascular deaths	124§	133	0.93	0.72–1.20	0.59
Total deaths with confirmed cause	205	216	0.95	0.79–1.15	0.60
Total deaths¶	217	227	0.96	0.80–1.14	0.64
Person-years of observation	54,894.6	54,864.2	—	—	—

*Numbers are code numbers of the *International Classification of Diseases*, ninth revision.

†All fatal cardiovascular events are included, regardless of previous nonfatal events.

‡This category includes ischemic (3 in the aspirin group and 3 in the placebo group), hemorrhagic (7 aspirin and 2 placebo), and unknown cause (0 aspirin and 2 placebo).

§This category includes one death due to gastrointestinal hemorrhage.

¶Additional events that could not be confirmed because records were not available included 23 deaths (12 aspirin and 11 placebo), of which 11 were suspected to be cardiovascular (7 aspirin and 4 placebo) and 12 noncardiovascular (5 aspirin and 7 placebo).

There were 169 participants with ulcer in the aspirin group and 138 in the placebo group (relative risk, 1.22; 95 percent confidence interval, 0.98 to 1.53; P = 0.08). Among those with ulcer, 38 of the participants taking aspirin experienced some hemorrhage, as compared with 22 taking placebo (relative risk, 1.77; 95 percent confidence interval, 1.07 to 2.94; P = 0.04).

With respect to bleeding, 2979 of the aspirin group and 2248 of those taking placebo reported problems such as easy bruising, hematemesis, melena, nonspecific gastrointestinal bleeding, epistaxis, or other bleeding (relative risk, 1.32; 95 percent confidence interval, 1.25 to 1.40; P<0.00001). Furthermore, 48 in the aspirin group and 28 in the placebo group required transfusion (relative risk, 1.71; 95 percent confidence interval, 1.09 to 2.69; P = 0.02). One death from gastrointestinal hemorrhage was reported. This occurred in the aspirin group, and the event was confirmed.

DISCUSSION

The results just described were virtually identical to the findings presented in our preliminary report.[9] Overall, there was a statistically significant, 44 percent reduction in the risk of myocardial infarction that included significant benefits of aspirin for both fatal and nonfatal events. There continued to be an apparent but not significantly increased risk of stroke — primarily in the subgroup of all hemorrhagic strokes — associated with the use of aspirin. In the subgroup of moderate-to-severe or fatal hemorrhagic stroke, the increased risk that we had observed previously was no longer statistically significant (13 events in the aspirin group and 6 in the placebo group; P = 0.11). No reduction in the risk of mortality from all cardiovascular causes was associated with aspirin. Our findings regarding stroke and cardiovascular mortality must be viewed in the context of the fact that the trial had too few events to evaluate either of these end points.

Even in a trial with our large sample, the ability to identify particular subgroups of participants more or less likely to benefit from aspirin is limited. We observed no significant modification of the effects of aspirin on any of the major manifestations of cardiovascular disease across the various risk-factor subgroups classified according to cigarette smoking, the history of diabetes mellitus, parental myocardial infarction, diastolic blood pressure, systolic blood pressure, alcohol use, amount of exercise, and body-mass index. The reduction in the risk of myocardial infarction associated with aspirin was apparent only among those 50 or older. More important, however, was the low absolute risk of myocardial infarction at younger ages, suggesting that any net benefit of aspirin would be greatest among physicians 50 years of age and older. For cholesterol, the beneficial effects of aspirin were apparent at all levels. The observation that the benefits of aspirin for myocardial infarction were greatest at low levels of cholesterol was unexpected. This observation may be correct or may reflect random fluctuations in the data from which it was derived. It is not possible on the basis of the present data to decide between these explanations. For stroke and cardiovascular mortality, there was no apparent modification of the effects of aspirin according to risk factors, with the possible exception of cigarette smoking (in relation only to cardiovascular mortality). The number of these end points was too small for us to detect whether overall results were meaningful; the analysis of these end points according to subgroup was therefore particularly difficult.

The only other randomized trial of the role of aspirin in the primary prevention of cardiovascular disease is a smaller study of British doctors.[13] In contrast to the Physicians' Health Study, the British Doctors' Trial showed no significant differences for fatal or nonfatal myocardial infarction, but the 95 percent confidence intervals were very wide. As in the Physicians' Health Study, there were more strokes among those assigned to aspirin, although the difference was not significant, and there was no significant difference in mortality from all cardiovascular causes. There were differences in the design of the U.S. and British trials, including the doses (325 mg on alternate days vs. 500 mg daily), blinding (double-blind with placebo control vs. single-blind), compliance (85.71 percent in the aspirin group and 85.74 percent in the placebo group after 60.2 months vs. 70 percent in the aspirin group and 98 percent in the group without aspirin after 36 months of a 72-month follow-up), and definition of end points. Perhaps most relevant, however, was the difference in the sample size; 5139 subjects were randomly assigned to aspirin or control in the British

Table 4. Risk of Total Myocardial Infarction Associated with Aspirin Use, According to Level of Coronary Risk Factors.

	Aspirin Group	Placebo Group	Relative Risk	P Value of Trend in Relative Risk
	no. of myocardial infarctions/total no. (%)			
Age (yr)				
40–49	27/4527 (0.6)	24/4524 (0.5)	1.12	
50–59	51/3725 (1.4)	87/3725 (2.3)	0.58	0.02
60–69	39/2045 (1.9)	84/2045 (4.1)	0.46	
70–84	22/740 (3.0)	44/740 (6.0)	0.49	
Cigarette smoking				
Never	55/5431 (1.0)	96/5488 (1.8)	0.58	
Past	63/4373 (1.4)	105/4301 (2.4)	0.59	0.99
Current	21/1213 (1.7)	37/1225 (3.0)	0.57	
Diabetes mellitus				
Yes	11/275 (4.0)	26/258 (10.1)	0.39	0.22
No	128/10,750 (1.2)	213/10,763 (2.0)	0.60	
Parental history of myocardial infarction				
Yes	23/1420 (1.6)	39/1432 (2.7)	0.59	0.97
No	112/9505 (1.2)	192/9481 (2.0)	0.58	
Cholesterol level (mg per 100 ml)*				
<159	2/382 (0.5)	9/406 (2.2)	0.23	
160–209	12/1587 (0.8)	37/1511 (2.5)	0.29	0.04
210–259	26/1435 (1.8)	43/1444 (3.0)	0.61	
≥260	14/582 (2.4)	23/570 (4.0)	0.59	
Diastolic blood pressure (mm Hg)				
≤69	2/583 (0.3)	9/562 (1.6)	0.21	
70–79	24/2999 (0.8)	40/3076 (1.3)	0.61	0.88
80–89	71/5061 (1.4)	128/5083 (2.5)	0.55	
≥90	26/1037 (2.5)	43/970 (4.4)	0.56	
Systolic blood pressure (mm Hg)				
<109	1/330 (0.3)	4/296 (1.4)	0.22	
110–129	40/5072 (0.8)	75/5129 (1.5)	0.52	0.48
130–149	63/3829 (1.7)	115/3861 (3.0)	0.55	
≥150	19/454 (4.2)	26/412 (6.3)	0.65	
Alcohol use				
Daily	26/2718 (1.0)	55/2727 (2.0)	0.45	
Weekly	70/5419 (1.3)	112/5313 (2.1)	0.61	0.26
Rarely	40/2802 (1.4)	65/2897 (2.2)	0.63	
Vigorous exercise at least once a week				
Yes	91/7910 (1.2)	140/7861 (1.8)	0.65	0.21
No	45/2997 (1.5)	92/3060 (3.0)	0.49	
Body-mass index†				
≤23.0126	26/2872 (0.9)	41/2807 (1.5)	0.61	
23.0127–24.4075	32/2700 (1.2)	46/2627 (1.8)	0.68	0.90
24.4076–26.3865	32/2713 (1.2)	75/2823 (2.7)	0.44	
≥26.3866	49/2750 (1.8)	76/2776 (2.7)	0.65	

*To convert cholesterol value to millimoles per liter, multiply by 0.02586.

†Body-mass index is the weight (in kilograms) times the height (in meters) squared.

trial, and 22,071 in the U.S. study. To minimize the effect of this difference in sample size, we undertook an overview of the two trials of primary prevention.[14] Since the U.S. trial was so much larger, this overview showed a significant, 33 percent reduction in nonfatal myocardial infarction associated with aspirin ($P<0.0002$). A repeated analysis, in which data from this final report were used, gave virtually identical results.

The findings of this study of aspirin in the primary prevention of cardiovascular disease should be viewed in the context of all the evidence concerning the possible role of aspirin. In 1985 the Food and Drug Administration approved the labeling of aspirin as an agent to be prescribed for the treatment of patients with a previous myocardial infarction or unstable angina.[15] A recent overview[16] of 25 randomized trials of antiplatelet therapy (aspirin, dipyridamole, or sulfinpyrazone, alone or in combination) in patients with a history of cardiovascular disease demonstrated a 25 percent reduction in the incidence of subsequent important vascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease), a 32 percent decrease in nonfatal myocardial infarction, a 27 percent reduction in nonfatal stroke, and a 15 percent reduction in cardiovascular mortality. All these reductions were statistically significant. Moreover, aspirin was at least as effective as dipyridamole or sulfinpyrazone. Most recently, the Second International Study of Infarct Survival[17] evaluated the role of aspirin in evolving myocardial infarction in a randomized trial with 17,187 participants and demonstrated a 49 percent reduction in nonfatal myocardial infarction, a 46 percent decrease in nonfatal stroke, and a 23 percent reduction in cardiovascular death after five weeks. All these reductions were statistically significant.

Aspirin's benefits in reducing the incidence of subsequent myocardial infarction have been shown conclusively in the survivors of myocardial infarction and stroke and in patients with unstable angina, as well as in those with an evolving heart attack. Our trial demonstrates conclusively a benefit of aspirin in reducing the incidence of first myocardial infarction and thus extends the previous findings to healthy people. Benefits in reducing the incidence of subsequent stroke have been shown conclusively in survivors of myocardial infarction and stroke and in patients with unstable angina, as well as in those with an evolving heart attack. The findings of our trial of primary prevention, although not statistically significant, are compatible with an increase in the number of all strokes among aspirin users. It seems important to distinguish between ischemic stroke, in which one might expect aspirin to be of benefit, and hemorrhagic stroke, in which one might expect an adverse effect. The possibility of an increase in the incidence of hemorrhagic stroke among aspirin users is not unexpected, since any agent that decreases clotting may help prevent ischemic events but increase bleeding. To evaluate this matter further, future trials in which the sample size is adequate to distinguish between ischemic and hemorrhagic stroke are required.

Finally, aspirin's benefits in reducing the incidence of cardiovascular mortality have been shown con-

Table 5. Side Effects According to Treatment Group.

SIDE EFFECT*	ASPIRIN GROUP	PLACEBO GROUP	P VALUE
	number/percent		
Gastrointestinal symptoms (except ulcer)	3843 (34.8)	3779 (34.2)	0.48
Discomfort (535)	2882 (26.1)	2823 (25.6)	0.45
Other noninfectious disorders of the digestive tract (536, 537.8, 537.9)	345 (3.1)	288 (2.6)	0.02
Miscellaneous symptoms of the digestive tract (533.123, 787, 789.0)	2384 (21.6)	2405 (21.8)	0.75
Upper gastrointestinal ulcers	169 (1.5)	138 (1.3)	0.08
Esophageal ulcer (530.2)	11 (0.1)	6 (0.05)	0.23
Gastric ulcer (531)	25 (0.2)	15 (0.1)	0.11
Duodenal ulcer (532)	46 (0.4)	27 (0.2)	0.03
Peptic ulcer (533)	156 (1.4)	129 (1.2)	0.11
Gastrojejunal (534)	3 (0.03)	4 (0.04)	0.70
Bleeding problems	2979 (27.0)	2248 (20.4)	<0.0001
Easy bruising (459)	1587 (14.4)	1027 (9.3)	<0.0001
Hematemesis (578.0)	38 (0.3)	28 (0.3)	0.22
Melena (578.1)	364 (3.3)	246 (2.2)	<0.00001
Nonspecific gastrointestinal bleeding (578.9)	440 (4.0)	422 (3.8)	0.55
Epistaxis (784.7)	862 (7.8)	640 (5.8)	<0.0001
Other bleeding† (599.7, 958.2)	724 (6.6)	596 (5.4)	0.0004

*Numbers in parentheses are code numbers of the *International Classification of Diseases*, ninth revision.

†Twenty-nine percent were related to shaving or brushing the teeth (32 percent aspirin and 27 percent placebo), and 72 percent were hematuria (70 percent aspirin and 75 percent placebo).

clusively in the survivors of myocardial infarction and stroke and in patients with unstable angina, as well as in those with an evolving heart attack. In our trial of primary prevention, however, no reduction in the risk of mortality from all cardiovascular causes was associated with aspirin. Although it may be tempting to speculate about possible explanations for this finding, the primary consideration must be that the cardiovascular mortality rate among the physicians in this trial was only 15 percent of that expected for a general population of white men with the same age distribution over a similar period. This reduction was even greater than our conservative estimates of the "healthy volunteer"[6] effect had suggested. The chief consequence of this extremely low cardiovascular mortality rate was to render it impossible to detect reliably whether aspirin had any effect on total mortality from cardiovascular causes until at least the year 2000. In addition, over 85 percent of the participants who had a nonfatal myocardial infarction were being treated with aspirin, making any finding about cardiovascular mortality particularly difficult to interpret.

The side effects of aspirin are clearly related to the size of the dose. The Aspirin Myocardial Infarction Study[18] tested a dose of 1000 mg a day, and gastrointestinal symptoms were reported by 23.7 percent of those assigned to active treatment and 14.9 percent of those assigned to placebo. In the recently completed United Kingdom Transient Ischemic Attack trial,[2] those receiving 300 mg daily experienced 30 percent fewer side effects than those receiving 1200 mg — a significant reduction ($P<0.0001$). In the Physicians' Health Study, in which the dose was 325 mg on alternate days, the rate of gastrointestinal discomfort attributable to aspirin was relatively low (0.5 percent). As expected, increased risks of upper gastrointestinal ulcers and bleeding problems were attributable to aspirin in this trial. Of greater clinical relevance, however, were their relatively low rates of occurrence, due in part to the low dose and the frequency of administration, and also to our eligibility criteria and the prerandomization run-in phase of the study, which excluded participants unable to tolerate the drug.[9] For all these reasons, the frequency and severity of gastrointestinal discomfort, ulcers, and bleeding complications attributable to aspirin were far lower than those reported in previous trials.

There is some suggestion that low doses of aspirin are at least as effective in reducing the risk of cardiovascular disease as high doses. An overview of the trials of secondary prevention indicated that patients receiving 300 mg a day gained the same beneficial effect as those receiving 1500 mg.[16] The benefits of aspirin observed in both the Second International Study of Infarct Survival[17] and the Physicians' Health Study resulted from low-dose therapy — 160 mg daily and 325 mg every other day, respectively. A dose of 325 mg of buffered or enteric-coated aspirin every other day completely inhibits platelet aggregation, with no recovery even 48 hours after the last dose.[19] Pharmacologic studies have suggested that the dose of aspirin necessary to inhibit platelet aggregation may be lower than 80 mg.[20] However, in the acute stage of a cardiovascular event (unstable angina, transient ischemic attack, or myocardial infarction), a dose of about 160 mg to give a more rapid antithrombotic effect might be prudent.[17]

Since both trials of aspirin in primary prevention were confined to men, there is no direct evidence on the role of aspirin in the primary prevention of cardiovascular disease in women. Both the overview[15] and the Second International Study of Infarct Survival[17] demonstrated aspirin's significant benefits for secondary prevention of the various manifestations of cardiovascular disease in women. One can consider generalizing the results of our primary-prevention trial to women, but any such clinical judgment must take into account their absolute risks of various cardiovascular events as well as the possibility that aspirin in low doses may have a different pharmacologic effect in women.[21] The only way to evaluate this question directly is through a randomized trial of healthy women that has a sufficiently large sample to detect the most plausible small-to-moderate effects.

Since the publication of our preliminary report, 74 percent of the participating physicians who were assigned to placebo have requested that their calendar packs be changed to aspirin. For the general public, however, the decision whether to take aspirin to reduce the risks of cardiovascular disease should be an individual judgment made only with the advice of a physician or other health care provider. In the making

of this decision, the cardiovascular risk profile of the patient and the risks and benefits of the drug should be weighed.

The dedicated and conscientious collaboration of our study's 22,071 physicians has provided important information and has made it possible to conduct the trial at a small fraction of the usual cost. With the continued commitment of the participating physicians, we shall collect more observational data on stroke and cardiovascular mortality. In addition, the ongoing randomized component of the trial should provide important information on the possible role of beta carotene in the prevention of cancer.

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