Clinical Characteristics of Nonfatal Myocardial Infarction Among Individuals on Prophylactic Low-Dose Aspirin Therapy

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Background. The influence of prophylactic low-dose aspirin on the clinical characteristics of subsequent nonfatal myocardial infarction was examined in the Physicians’ Health Study, a randomized, double-blind placebo-controlled trial of alternate-day aspirin (325 mg) among 22,071 US male physicians.

Methods and Results. During 60.2 months of follow-up, 342 incident cases of nonfatal myocardial infarction were confirmed (95.2% of all reports): 129 on aspirin and 213 on placebo ($p<0.00001$). Despite this statistically extreme reduction in occurrence of a first nonfatal infarction attributable to aspirin, there were no significant differences in the size, location, electrocardiographic features, or postinfarction left ventricular ejection fraction between the aspirin and placebo groups. Furthermore, among those undergoing angiography, there were no differences in the distribution or number of coronary vessels obstructed.

Conclusions. These data indicate that chronic platelet inhibition with alternate-day aspirin therapy reduces the risk of a first myocardial infarction but does not appear to have a significant effect on the clinical characteristics of events that are survived. This finding may result from a direct effect of aspirin or from an aspirin-induced shift in infarction severity. Regardless of mechanism, these clinical observations suggest that treatment decisions for acute infarction patients should be made independently of a history of aspirin use. (Circulation 1991;84:708–711)

Low-dose aspirin therapy reduces the risk of acute myocardial infarction among patients with a history of myocardial infarction, stroke, or unstable angina as well as among apparently healthy individuals. In experience of experiencing reduced risk, it is possible that patients suffering infarction while on chronic aspirin therapy have fewer complete coronary occlusions, achieve earlier reperfusion, and sustain smaller infarctions. On the other hand, it is possible that prophylactic aspirin decreases the risk of acute coronary closure but has little effect on the characteristics of infarctions that ultimately occur. Despite the fact that these issues are important for patient management, there are currently no data examining the effects of chronic platelet inhibition with low-dose aspirin on the clinical characteristics of nonfatal myocardial infarction.

In the Physicians’ Health Study, 22,071 apparently healthy males 40–84 years old were randomized to 325 mg of alternate-day aspirin ($n=11,037$) or placebo ($n=11,034$) therapy and were followed for an average period of 60.2 months. In this report, we describe and compare the size, location, and clinical characteristics of nonfatal myocardial infarctions among those assigned at random to low-dose aspirin with those given placebo.

Methods

A detailed description of the subjects and methods of the Physicians’ Health Study has previously been reported. Briefly, 22,071 US male physicians free of prior myocardial infarction, transient ischemic attack, or stroke were randomized in 1982 to either 325 mg of alternate-day aspirin therapy or aspirin placebo. Every 6 months for the first year and annually thereafter, participants were mailed questionnaires asking about their compliance with the study drug
and any changes in health status. The randomized aspirin component of the Physicians' Health Study was terminated early because a statistically extreme reduction in occurrence of a first myocardial infarction was found among those assigned aspirin. At this time, subjects had been followed for an average of 60.2 months, vital status was known for all participants, data on morbidity were 99.7% complete, and hospital records were available for more than 95% of reported cardiovascular events.

All reported end points of myocardial infarction were confirmed by a committee of physicians masked to treatment assignment using standard World Health Organization criteria.\(^6\) Three hundred forty-two incident cases of first nonfatal acute myocardial infarction were reported and confirmed: 129 on aspirin therapy and 213 on placebo. Clinical characteristics of these infarctions were determined by further review of hospital charts by a physician (P.M.R.) also blinded to treatment assignment.

The size and severity of infarctions were estimated by analyzing peak creatine kinase (CK) and CK-MB isoenzyme levels and, when available, through comparisons of postinfarction left ventricular function as measured by radionuclide ventriculography, echocardiography, or left ventriculography at catheterization. Electrocardiograms were reviewed using standard criteria to determine anatomic localization of infarction and the presence or absence of Q waves. When multiple sites of infarction were present, all were included in the analyses. For example, an interposterior infarction was tabulated as both inferior and posterior.

Cardiac catheterization reports, when available, were reviewed to determine the extent of atherosclerotic lesions in the right, left anterior descending, left circumflex, and left main coronary arteries. A lesion of 70% or greater was considered a significant obstruction. Lesions greater than 50% were considered significant if they occurred in the left main coronary artery.

### Statistical Analyses

To compare baseline characteristics of the study groups, mean values or proportions for each clinical variable were calculated. The significance of any differences in mean values between the aspirin and placebo groups was tested using the Student's \(t\) test for independent means. For variables in which the distribution was not normal, the significance of any differences in means was tested using a nonparametric \(t\) test. The significance of differences in proportions was tested by \(\chi^2\). All probability values are two sided.

### Results

Baseline characteristics of the physicians randomized in this report are presented in Table 1 according to treatment status. As expected in a sample size of 22,071, baseline characteristics were virtually identical in the aspirin and placebo groups.

Table 2 presents data comparing clinical characteristics among the 342 cases of nonfatal myocardial infarction in the Physicians' Health Study. Overall, no significant differences were found between aspirin and placebo groups for any estimates of infarct size, severity, anatomic distribution, or residual myocardial function.

For CK, a mean peak CK level of 1,291.5 IU was found in the aspirin group compared with 1,356.3 IU in the placebo group \((p=0.69)\). Mean peak CK-MB isoenzymes were 145.0 and 142.8 IU in these two groups, respectively \((p=0.93)\).

Using pooled data from echocardiographic, radionuclide, and ventriculogram studies, the mean postinfarction left ventricular ejection fraction was 53.9% in the aspirin group and 52.1% in the placebo group \((p=0.42)\).

Electrocardiographic analyses revealed that 56.3% of infarctions in the aspirin group showed development of Q waves compared with 59.0% in the placebo group \((p=0.54)\). Involvement of the anterior electrocardiographic leads was found in 37.2% of infarctions in the aspirin group compared with 40.5% in the placebo group \((p=0.56)\). No significant differences were found in the distributions of inferior, lateral, and posterior infarctions. Overall, 9.3% of all infarctions in the aspirin group involved multiple sites compared with 10.8% in the placebo group \((p=0.66)\).

### Table 1. Comparison of Treatment Groups According to Baseline Cardiovascular Risk Factors at Time of Randomization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aspirin ((n=11,037))</th>
<th>Placebo ((n=11,034))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>53.2</td>
<td>53.2</td>
</tr>
<tr>
<td>Reported hypertension* (%)</td>
<td>11.8</td>
<td>12.0</td>
</tr>
<tr>
<td>Mean systolic BP (mm Hg)</td>
<td>126.2</td>
<td>126.1</td>
</tr>
<tr>
<td>Mean diastolic BP (mm Hg)</td>
<td>78.9</td>
<td>78.8</td>
</tr>
<tr>
<td>Reported high cholesterol(^1) (%)</td>
<td>5.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Mean cholesterol level (mg/dl)</td>
<td>212.0</td>
<td>212.0</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Mean body mass index (kg/m(^2))</td>
<td>24.9</td>
<td>24.9</td>
</tr>
<tr>
<td>History of angina pectoris (%)</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Parental history of MI (%)</td>
<td>13.0</td>
<td>13.1</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td>49.3</td>
<td>49.8</td>
</tr>
<tr>
<td>Past (%)</td>
<td>39.7</td>
<td>39.1</td>
</tr>
<tr>
<td>Current (%)</td>
<td>11.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Exercise frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean times per month</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Rarely or never (%)</td>
<td>13.5</td>
<td>13.8</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean drinks per week</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Rarely or never (%)</td>
<td>14.7</td>
<td>15.1</td>
</tr>
</tbody>
</table>

BP, blood pressure; MI, myocardial infarction.

*Hypertension is defined as systolic pressure greater than 160 mm Hg or diastolic pressure greater than 95 mm Hg or currently treated.

\(^1\)High cholesterol is defined as level greater than 260 mg/dl or treated currently; available in approximately one third of subjects.
Cardiac catheterization data revealed no statistically significant differences in the percentage of subjects with one-vessel, two-vessel, three-vessel, or left main coronary artery disease. Nearly half of all physicians undergoing peri-infarction catheterization had one-vessel coronary artery disease in both the aspirin and placebo groups.

Table 3 presents data for peak CK, CK-MB, and postinfarction left ventricular ejection fraction for the aspirin and placebo groups stratified by age. There was no evidence of effect modification in the relation between aspirin use and these clinical variables when the data were analyzed separately for younger and older patients.

**Discussion**

Although low-dose aspirin clearly reduces the incidence of first myocardial infarction, the data presented in this report indicate that 325 mg of alternate-day aspirin does not appear to affect the size, anatomic distribution, or functional outcome of events that are survived. Specifically, there were no significant differences in total CK activity or CK-MB fraction between the aspirin and placebo groups. Similarly, there were no significant differences in proportions of Q wave and non-Q wave infarctions or in the distribution of subjects with one-vessel, two-vessel, three-vessel, and left main coronary artery disease. Further, the anatomic distribution of infarction as determined by electrocardiographic analysis showed no evidence that chronic aspirin therapy alters the location of myocardial infarction. Finally, no significant difference in residual left ventricular function after infarction was found between aspirin and placebo groups. For CK, CK-MB, and left ventricular ejection fraction, there was no apparent modification of the overall effect when data were analyzed in various age categories.

The finding that chronic platelet inhibition with low-dose aspirin reduces the incidence of nonfatal infarction but not the clinical characteristics of these events has relevance for patient management. Although the 11,037 men randomized to aspirin suffered 40% fewer nonfatal infarctions than the 11,034 assigned to placebo, the CK and CK-MB levels associated with these infarctions were virtually identical in the two treatment groups. Furthermore, there is no evidence that aspirin altered the frequency of Q wave infarction or led to a significant change in postinfarction left ventricular ejection fraction. Therefore, we believe that treatment decisions regarding acute myocardial infarction care should be made independently of a history of aspirin use. With respect to further doses of aspirin sufficient to maintain a prolonged antithrombotic effect, data from the ISIS-2 trial have clearly demonstrated that low-dose aspirin begun within 24 hours of the onset of suspected evolving myocardial infarction significantly reduces mortality by 23%.

Because hospital records were often incomplete for fatal events, the current study is limited to an analysis of nonfatal myocardial infarction. Thus, although chronic aspirin therapy does not appear to alter the clinical characteristics of nonfatal events, one must be cautious in drawing conclusions from these data regarding the effects of aspirin prophylaxis on all myocardial infarctions. In fact, it is quite possible that aspirin does reduce the size and severity of all infarctions but that in an analysis limited to nonfatal events, the difference is masked. For exam-
ple, aspirin therapy may result in a shift of fatal events to severe nonfatal events, severe events to mild events, and mild events to no event. In this situation, the resulting distribution of nonfatal infarctions may appear unchanged from placebo not because of a lack of effect but rather because some events are selectively omitted from the aspirin group.

The possibility of such a phase shift occurring has rarely been considered in previous clinical trials evaluating only nonfatal outcomes. In this trial, the case fatality rate for those suffering myocardial infarction while on aspirin appeared somewhat lower than for those on placebo (7.2% versus 10.9%), suggesting that a phase shift in severity may in fact be present. However, such a phase shift would not affect the validity or generalizability of the current findings because the clinical implications of this report concern all survivors of myocardial infarction who were on prophylactic aspirin at the time of their event.

Two potential limitations of the current data should be considered. First, comprehensive clinical information was not available on all 342 infarctions, raising the question of a possible bias that could occur if clinical data were selectively omitted by treatment group. However, for each clinical variable measured, the percentage of cases with available information was similar for the aspirin and placebo groups. Furthermore, systematic omission of data in this trial is highly unlikely because study subjects, hospital physicians, and the medical record reviewer were all blinded to treatment status.

Second, although the Physicians’ Health Study followed 22,071 individuals over a 5-year period, the possibility that the lack of a significant difference between aspirin and placebo groups is a result of a type II error must be considered. This may be a particular problem for postinfarction left ventricular ejection fraction, where data were not available for a substantial proportion of subjects. Even for this infrequently measured variable, however, the power to assess a 10% change resulting from aspirin therapy was more than 95% (two-sided α, 0.05).

Thus, although data from the Physicians’ Health Study demonstrate that alternate-day aspirin reduces the risk of first myocardial infarction, the current analyses also suggest that for survivors of these events, the clinical characteristics of acute infarction are not significantly changed by prior aspirin use. Therefore, the clinical decision to use adjuvant therapies directed at improving coronary patency and ventricular function in the postinfarction period should be made independent of a history of aspirin use.

Acknowledgments

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References


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