A Case-Control Study of Regular Aspirin Use and Coronary Deaths

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SUMMARY Information was collected for a large number of coronary risk factors on a series of 568 married, white men, aged 30–70 years, who died from coronary heart disease (CHD). However, conflicting results have been reported in epidemiologic studies of this association. In a hospital-based case-control study of non-fatal myocardial infarction (MI), the risk ratio of MI among regular aspirin users (defined as taking aspirin four or more days per week) was 0.53 that of non-users, a finding which indicated a protective effect of regular aspirin intake upon MI. In a randomized clinical trial of aspirin therapy among survivors of MI, the results were not statistically significant but were compatible with a small protective effect of aspirin which increased with duration of use. In contrast, the results of a large prospective cohort study of deaths due to coronary heart disease indicated no association with aspirin use. This report evaluates from retrospective data whether there is an association between regular aspirin intake and coronary deaths. The design uses male subjects who died as a result of CHD. Neighbors of these men are used as controls.

Methods

Study Population

The study population of cases and controls was restricted to married white men age 30–70 residing in two Florida counties. Subjects were identified by weekly reviews of death certificates during a 16 month period. Only men whose deaths were attributed to CHD within 24 hours after onset of symptoms were included.

One living control, individually matched as to age within the same decade (i.e., 30–39, 40–49, etc.) and neighborhood of residence, was selected for each case by a systematic household survey.

Of 1,019 wives of eligible patients, 174 were non-respondents and an additional 196 had to be excluded due to non-cooperation. The final study population consisted of 649 case-control pairs. Of these 649 pairs, 81 were excluded because of missing or unknown values, so that the data analysis are based on 568 case-control pairs.

Procedures

Letters of introduction were sent to the wives of eligible patients. An interviewer telephoned the wives to obtain an interview, which was conducted in the home between two weeks to two months after the death of the patient. For each wife of a case interviewed, a wife of a control was also interviewed. The interviewer asked questions concerning the husband's aspirin consumption during the three months before death for the case and for the control, as well as questions about other coronary risk factors. More detailed descriptions have appeared in a previous publication.

Methods of Data Analysis

The aspirin variable was measured by asking whether aspirin was consumed daily or weekly and, if so, how many tablets were taken. Regular aspirin users were defined as those who took aspirin at least four days per week. Initially, we calculated the matched pair risk ratio to quantitate the crude association between regular aspirin intake and coronary deaths.
To control for possible additional confounding variables, we used a recently-developed method of analysis of matched pair studies, which maintains the matching and allows for the control of additional confounding variables. In this method, a multiple logistic regression analysis within pair differences for all available variables is consecutively entered into the logistic equation in decreasing order of strength of the association with the dependent variable, in this case use or non-use of aspirin. When these other variables are included in the logistic equation, the residual association between aspirin use and coronary deaths is evaluated according to whether the regression constant significantly differs from zero. Unlike most multiple regression models where the chief aim is to estimate the regression coefficients and test them for statistical significance, in this method we estimate the regression constant and its standard error. To describe the association between regular aspirin intake and coronary deaths, we calculated an adjusted risk ratio. We defined the risk ratio as the ratio of the likelihood that a case took aspirin and the control did not, to the likelihood that the control took aspirin and the case did not. For each risk ratio estimate we calculated 95% confidence limits.

**Results**

Table 1 shows the results of various crude matched pair risk ratio estimates and their 95% confidence limits. For the total series of 568 case-control pairs, there were 94 in which the case was an aspirin user and the control was not, and 92 in which the control was an aspirin user and the case was not. The risk ratio estimate was, therefore, 1.0 (95% two-sided confidence limits 0.9 to 1.1).

To determine whether this result was affected by the presence or absence of prior CHD among cases, we obtained additional crude matched pair risk ratio estimates, the first among the 312 pairs without prior CHD, and the second among the 233 pairs with a prior history of CHD (23 pairs where the control had a prior history of CHD and the case had no such history were excluded). These estimates were 0.9 (0.6–1.3) and 1.3 (0.8–2.2), respectively.

Table 2 shows the results of the paired multiple logistic regression analyses for the 568 pairs, specifically, the variables significantly associated with the within pair differences for aspirin intake. These variables are first, use of additives (i.e., milk, cream, non-dairy creamer) with coffee or tea, followed in order by current cigarette smoking, history of elevated cholesterol, history of diabetes mellitus and relative weight (based on the Framingham classification)

Table 3 shows various adjusted risk ratio estimates and their 95% confidence limits. After controlling for other variables, the adjusted matched pair risk ratio estimate for coronary deaths among aspirin users in the total series was 1.4 (0.9–2.1). For those without prior CHD, the risk ratio estimate was 1.1 (0.7–1.8), whereas for those where the case had prior CHD, the estimate was 1.4 (0.9–2.2).

**Discussion**

These findings show no evidence of association between regular aspirin intake and coronary death and, therefore, do not support the hypothesis of a preventive role of aspirin in CHD. Furthermore, as shown in table 3, the adjusted risk ratio estimates are all greater than one, indicating that observed differences are not even in the direction of possible benefit.

These results from a case-control study are consistent with those of Hammond and Garfinkel from their prospective cohort study. In that survey of over one million people, CHD rates were no lower among people who took aspirin "often" than among those who did not.

The data from the present investigation are based on deaths due to CHD within 24 hours after the onset of symptoms as indicated on death certificates. In contrast, Jick et al. found a protective effect of aspirin, using cases of non-fatal MI and hospitalized controls. Questions may be raised about the suitability of the selection of both the patients and controls in that study. An unknown fraction of patients hospitalized less than 72 hours were missed because of time lags between patient admissions and interviews. This selection is reflected in the finding that only 4% of patients studied died in the hospital, as compared with frequencies of 20–30% for hospitalized acute MI in general.

**Table 1. Matched Pair Risk Ratio Estimates for Coronary Deaths Among Regular Aspirin Users Versus Non-users**

<table>
<thead>
<tr>
<th>Total number of pairs</th>
<th>Number of discordant pairs</th>
<th>Risk ratio</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total series</td>
<td>568</td>
<td>156</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>0.7–1.3</td>
</tr>
<tr>
<td>No prior CHD</td>
<td>233</td>
<td>58</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.3</td>
<td>0.8–2.2</td>
</tr>
<tr>
<td>Prior CHD</td>
<td>312</td>
<td>125</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9</td>
<td>0.6–1.3</td>
</tr>
</tbody>
</table>

**Table 2. Variables Significantly Associated with Aspirin Intake Among 568 Case-control Pairs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>+0.332</td>
<td>0.197</td>
<td>NS</td>
</tr>
<tr>
<td>Additives to coffee or tea</td>
<td>−0.841</td>
<td>0.250</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Current cigarettes</td>
<td>+0.719</td>
<td>0.237</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Elevated cholesterol</td>
<td>+1.007</td>
<td>0.480</td>
<td>P = 0.006</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−1.290</td>
<td>0.536</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Relative weight</td>
<td>+1.010</td>
<td>0.516</td>
<td>P = 0.05</td>
</tr>
</tbody>
</table>

**Table 3. Adjusted Risk Ratio Estimates for Coronary Deaths Among Regular Aspirin Users Versus Non-users**

<table>
<thead>
<tr>
<th>Total number of pairs</th>
<th>Risk ratio</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total series</td>
<td>568</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9–2.1</td>
</tr>
<tr>
<td>No prior CHD</td>
<td>312</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7–1.8</td>
</tr>
<tr>
<td>Prior CHD</td>
<td>233</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9–3.3</td>
</tr>
</tbody>
</table>

Abbreviation: CHD = coronary heart disease.
An additional selection occurred before admission, since about 60% of MI patients die before getting to a hospital.11 These patients, therefore, are a highly selected subgroup of the total number of patients who experience MI. It is possible that aspirin intake is unrelated to the onset of MI, but favors survival following the event.

The controls were patients admitted to the hospitals for a variety of conditions, any of which may have had positive associations with aspirin. Aspirin may cause some conditions, such as gastrointestinal disturbances. The chronic persistence of other conditions, such as arthritis or headache, may have led some controls to take aspirin. Nevertheless, in the Jick study, subjects with a secondary diagnosis of these conditions were not excluded. This previous study, therefore, is an example of the selection bias of hospital data (Berkson's fallacy).12 The underlying concept is that in the general population in which disease is incident, the variable "hospitalization" has the associations with exposure and outcome characteristic of a confounding variable, but it is not a confounding variable because it is an effect of exposure. It should not, therefore, be "controlled" by restriction, that is, by limiting the study to the hospitalized group.

The results of the randomized case-control study of Elwood et al.3 showed a small protective, though nonsignificant, effect of aspirin on the recurrence of MI. In the present investigation, there is no evidence of a protective effect of aspirin, even when restricting our analyses to those pairs where the case had a prior history of CHD and the control did not. This finding is compatible with the results of a clinical investigation by Frishman et al., who found no effect of aspirin on the reduction of anginal pain during exercise.

The validity of the findings of the present study may be affected by at least two possible sources of bias, namely, selection and observation.

**Selection Bias**

A potential source of bias exists in the selection of wives for interview, in that the wives of patients may have been more or less available for interview than the wives of controls. Insofar as availability is associated with the husband's aspirin consumption, a systematic error in either direction could result.

It is also possible that selection bias may have occurred in this design due to the use of death certificate diagnoses of death from coronary disease. A previous paper showed that in a special autopsy series of sudden (within one hour after onset), unexpected deaths in white males, the medicolegal diagnosis of CHD was justified in 90% of the cases.14 In a more general group of deaths, Moriyama et al. found that for about 80% of diagnoses relating to sudden death, the certified diagnoses should be classified as "reasonable inference" or better, although in many of these cases information was sketchy, and that for all deaths classified as CHD, 70-75% of the diagnoses should be similarly classified.15 More recently, Moriyama et al. concluded, "Because there are few diseases other than CHD which are frequent causes of sudden, unexpected death, it is reasonable to attribute such deaths to CHD."16 With respect to the present investigation, a selection error, if unbiased for aspirin intake, would not dilute the true association. A biased selection error would dilute the true effect only if patients incorrectly included in the study were more similar to controls than patients with true CHD. To explore the possibility of bias and its direction in the data, we compared the frequency of regular aspirin intake of 365 death certified patients without autopsy confirmation (19.7%), 203 patients with confirmation (17.2%) and 568 controls (18.5%). The difference is in the direction of diluting the true association, but it is too small to alter the estimate of the risk ratio.

**Observation Bias**

A second potential source of bias is that wives may not accurately report the aspirin intake of their husbands. This inaccuracy may have been systematically different for cases and controls, since subjects had died and controls were alive. Depending on whether wives thought that using aspirin was either unhealthy or healthy, they may have either over- or underestimated their husband's aspirin consumption. Wives of controls might have also over- or underestimated their husband's aspirin consumption. This systematic error would lead to either an under- or overestimate of the protective effect of aspirin. A systematic inaccuracy in the opposite direction could also be supposed. Since we collected information from the husbands of 48 control wives about their own aspirin intake, we were able to determine whether this potential source of bias was present among controls. The husbands and wives reported very similar frequencies of regular aspirin intake (20.8% and 18.8%, respectively). It was, of course, not possible to evaluate this potential source of bias among cases.

In summary, these findings from retrospective data provide no evidence of a protective role of regular aspirin use in coronary deaths either among patients with or without a history of CHD. To further clarify this relationship, it will be important to compare results from several investigations using different study designs. In that regard, the outcome of the ongoing Aspirin Myocardial Infarction Study (AMIS), a cooperative, randomized clinical trial, will be particularly informative.

**Acknowledgment**

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**References**

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