

## Clinical Problems

# Aspirin and Coronary Heart Disease: Findings of a Prospective Study

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### Summary

**Over 1 000 000 men and women answered a confidential questionnaire and were traced for up to six years afterwards. Among other questions each person was asked how often he or she took aspirin—"never," "seldom," or "often." Coronary heart disease death rates were no lower among people who took aspirin often than among those who did not do so.**

### Introduction

We undertook this study because of two papers which appeared in the *British Medical Journal* in 1974.<sup>1,3</sup> Both suggested that daily use of aspirin reduces the risk of myocardial infarction. One was a retrospective epidemiological study and the other a clinical trial. The results of the latter, though in the indicated direction, were not statistically significant, and the authors refrained from drawing firm conclusions. Hence we analysed pertinent data already on hand from a prospective epidemiological study.

### Subjects and Methods

Starting on 1 October 1959 volunteer workers of the American Cancer Society enrolled over 1m. men and women as subjects for a long-term study. All were over the age of 30 and most were over 45. On enrollment each subject answered a long confidential questionnaire, which included questions on family history, disease history, physical complaints, habits, and many other factors. The subjects were traced up to 30 September 1965, and death certificates were obtained on those who died. Further details of the study and some findings in respect to coronary heart disease have been published.<sup>3-5</sup>

The initial questionnaire contained the question, "How often do you use the following types of medicine?" One of the medicines listed was "aspirin (Bufferin)" and the subject could tick "never," "seldom," or "often." Bufferin is a brand of aspirin widely advertised in the United States. The terms "never" "seldom" and "often" referred to current use rather than lifetime use. Most people ticked "seldom" (table I). Proportionately more women than men ticked "often," and the proportion ticking "often" increased with age. Conversely, proportionately more men than women ticked "never," but the overall proportion ticking "never" also increased with age.

Some people (2.4% of men and 3.0% of women) failed to

answer the question on aspirin. Thus our analysis was based on the records of 434 958 men and 558 038 women aged 35 and older who answered the question (table I). During the six years of observation 42 770 men and 28 941 women died. According to their death certificates 18 724 of the men and 8125 of the women died because of coronary heart disease—that is, coronary thrombosis, coronary occlusion, myocardial infarction, etc.

Subjects of each sex were divided into five-year age group cohorts according to age at start of study. Death rates were calculated for each cohort by dividing the number of deaths by person-years of exposure to risk during the period from 1 October 1959 to 30 September 1965. These rates were then applied to person-years of exposure of people in each aspirin-use category ("never," "seldom," and "often") to obtain the expected number of deaths in each of these three categories.

### Results

In the first analysis we excluded people who reported a history of heart disease, stroke, diabetes, or high blood pressure. The results in relation to coronary heart disease for all men, men who smoked 20 or more cigarettes a day, and all women are shown in table II. For each sex the observed number of deaths from coronary heart disease was slightly less than the expected number—that is a mortality ratio less than 1.00—among people who seldom took aspirin and slightly greater than the expected number among people who never took aspirin and those who often took aspirin.

Essentially the same relationships were found in respect to deaths ascribed to cerebral vascular lesions. For all deaths (disregarding cause) the mortality ratios were greater than 1.00 among people who often took aspirin.

Since these findings are very different from those in the published retrospective study,<sup>1</sup> we made several more analyses to see whether a different handling of the data would yield results more in line with that study. For example, one analysis was the same as that described above but confined to experience during the first 39 months of the study; another included all subjects regardless of past history of disease; another included all subjects but was confined to the 12-month period after the date of enrollment of each subject; and another was confined to the first six-month period. None of these analyses suggested that taking aspirin often was associated with a reduction of death rates from coronary heart disease.

At Dr. H. Jick's suggestion we analysed data on only those people who on the initial questionnaire had said that they had or had had heart disease (table III). Among women aged 35-49 the mortality ratio for the aspirin-often group was 0.67, but this ratio was based on small numbers. Among men aged 35-49 and those aged 50-64 the mortality ratios for the aspirin-often group were 0.95 and 0.92 respectively. Taken as a whole, however, the figures did not indicate that the use of aspirin often was associated with a reduced risk of death from coronary heart disease. Another analysis confined to people with a history

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TABLE I—Number of Men and Women Classified by Age and Use of Aspirin

Age (Years)	Men			Women		
	Aspirin Never	Aspirin Seldom	Aspirin Often	Aspirin Never	Aspirin Seldom	Aspirin Often
35—49	15 982	110 027	19 575	11 754	159 638	53 822
50—64	33 784	155 933	28 569	21 807	169 464	51 209
65—79	14 684	41 944	9 124	12 814	52 288	15 953
≥80	1 527	2 827	928	1 939	4 990	2 360

TABLE II—Observed and Expected Number of Deaths from Coronary Heart Disease and Mortality Ratios\* among Subjects with no Prior History of Heart Disease, Stroke, High Blood Pressure, or Diabetes

Age at Start of Study	Aspirin Never			Aspirin Seldom			Aspirin Often		
	No. Observed	No. Expected	Mortality Ratio	No. Observed	No. Expected	Mortality Ratio	No. Observed	No. Expected	Mortality Ratio
<i>Men</i>									
35—49	150	129.31	1.16	868	888.14	0.98	151	151.54	1.00
50—64	749	716.41	1.05	3168	3250.85	0.97	613	562.74	1.09
65—79	741	742.71	1.00	1998	2070.39	0.97	469	394.89	1.19
≥80	178	183.70	0.97	324	331.86	0.98	110	96.45	1.14
Total	1818	1772.13	1.03	6358	6541.24	0.97	1343	1205.62	1.11
<i>Men who smoked ≥20 Cigarettes a Day</i>									
35—49	100	79.51	1.26	562	578.34	0.97	103	107.15	0.96
50—64	316	289.04	1.09	1361	1420.94	0.96	306	272.93	1.12
65—79	120	101.21	1.19	332	353.26	0.94	87	84.53	1.03
≥80	4	5.98	0.67	11	10.12	1.09	5	3.90	1.28
Total	540	475.74	1.14	2266	2362.66	0.96	501	468.51	1.07
<i>Women</i>									
35—49	21	10.18	2.06	126	138.50	0.91	47	45.11	1.04
50—64	81	86.01	0.94	611	628.43	0.97	197	174.56	1.13
65—79	276	232.65	1.19	843	918.74	0.92	296	263.59	1.12
≥80	133	139.16	0.96	327	348.96	0.94	176	147.86	1.19
Total	511	468.00	1.09	1907	2034.63	0.94	716	631.12	1.13

\*Mortality ratio is observed number of deaths divided by expected number of deaths.

of heart disease but no past history of stroke, high blood pressure, or diabetes yielded results similar to those shown in table III.

Many people who took aspirin often may have taken it less often than once a day so, also at Dr. Jick's suggestion, we analysed the records of people who said that they had arthritis and took aspirin often. (He had found that people who take aspirin for arthritis generally take fairly large amounts daily). There were 55 808 such people in the study (14 401 men and 41 407 women). In every age group in both sexes the death rate from coronary heart disease was slightly higher than that for all subjects combined.

#### MATCHED-GROUPS ANALYSIS

It seemed likely that people who took aspirin often were as a group at least slightly different from other people in many ways, and this might have produced some bias in the results described above. We know of no way to eliminate completely

the possibility of bias but if present bias can generally be reduced by restricting variability. Thus we matched subjects who took aspirin often with subjects who did not do so. This procedure was a modified form of matched-pairs analysis.

The subjects were divided into sets, each set consisting of people who were alike (within specified limits) in sex, five-year age group, race, usual amount of exercise, relative weight, consumption of meat and eggs (high, low, or intermediate), smoking habits, coffee drinking, severe nervous tension (yes or no), use of tranquillizers, use of vitamin pills, education (high school graduate, yes or no); marital status, residence in a city (as opposed to suburb, town, or rural area), history of high blood pressure (yes or no), and history in respect to each of the follow-up diseases: cancer, heart disease, stroke, diabetes, and cirrhosis of liver. Within each set the subjects were divided into two groups—those who took aspirin often and those who did not take aspirin often. In most sets one of these two groups was larger than the other, and to adjust for this difference in size the observed number of deaths in the larger of the two groups was multiplied by the ratio of the number of subjects in the smaller groups: the

TABLE III—Observed and Expected Number of Deaths from Coronary Heart Disease and Mortality Ratios\* Among Subjects with Prior History of Heart Disease

Age at Start of Study	Aspirin Never			Aspirin Seldom			Aspirin Often		
	No. Observed	No. Expected	Mortality Ratio	No. Observed	No. Expected	Mortality Ratio	No. Observed	No. Expected	Mortality Ratio
<i>Men</i>									
35—49	75	59.72	1.26	303	314.85	0.96	67	70.42	0.95
50—64	565	485.53	1.16	1810	1854.46	0.98	394	429.00	0.92
65—79	511	523.52	0.98	1375	1413.25	0.97	422	371.24	1.14
≥80	100	90.63	1.10	170	179.39	0.95	66	66.00	1.00
Total	1251	1159.40	1.08	3658	3761.95	0.97	949	936.66	1.01
<i>Women</i>									
35—49	10	4.70	2.13	35	34.97	1.00	11	16.33	0.67
50—64	80	73.53	1.09	326	341.95	0.95	145	135.53	1.07
65—79	229	229.01	1.00	693	712.11	0.97	294	274.87	1.07
≥80	112	99.49	1.13	216	235.42	0.92	121	114.08	1.06
Total	431	406.73	1.06	1270	1324.45	0.96	571	540.81	1.06

\*Mortality ratio is observed number of deaths divided by expected number of deaths.

number of subjects in the larger group. The figures for all sets were then summarized. The result was equivalent to carrying out matched-pairs analysis many times over (each time using random numbers to select individual pairs within a set) and then averaging the results. The findings are described below, each figure being rounded off to the nearest whole number.

Among men there were 47 047 matched pairs (47 047 aspirin-often subjects matched with 47 047 aspirin not often subjects). During the study 4212 of the "often" subjects died and 3892 of the "not often" subjects died: 1756 of the "oftens" and 1726 of the "not oftens" died of coronary heart disease. Among women there were 102 049 matched pairs, and 4218 "oftens" and 3995 "not oftens" died: 1124 of the "oftens" and 1070 of the "not oftens" died of coronary heart disease. Thus the number of people of both sexes who died of coronary heart disease was slightly higher among those who took aspirin often than among those who did not take aspirin often.

Generally the reported cause of death may be less liable to error if death occurs in hospital than elsewhere. In the United States many deaths attributed to coronary heart disease occur out of hospital, this being commonly so in cases of sudden death. According to Spain,<sup>6</sup> recent coronary heart thrombi are seldom found at necropsy in sudden and unexpected fatalities from coronary heart disease. For these reasons place of death could have a bearing on interpretation of our findings.

Among men 862 of the "oftens" and 842 of the "not oftens" died in hospital of coronary heart disease; among women, 572 of the "oftens" and 539 of the "not oftens" so died. Among men 894 of the "oftens" and 884 of the "not oftens" died out of hospital of coronary heart disease, and among women 552 of the "oftens" and 531 of the "not oftens" so died.

## Discussion

The Boston Collaborative Drug Surveillance Group reported the results of two similar retrospective studies on use of aspirin in relation to risk of acute myocardial infarction.<sup>1</sup> Both studies covered patients admitted to hospital for myocardial infarction while controls consisted of patients admitted to hospital for some other condition, including angina pectoris or coronary insufficiency without evidence of acute myocardial infarction. Regular aspirin users were defined as patients who took aspirin daily (first study) or patients who took aspirin at least four days a week and continued to do so up to the time of admission (second study). The results seemed to indicate that the relative risk of acute myocardial infarction is about one-fifth as high (first study) or about half as high (second study) in regular aspirin users as in other people.

If such be the case it is reasonable to postulate that habitual use of aspirin four days or more a week would result in a substantial reduction in death rates from coronary heart disease. A direct test of this hypothesis would require information on how many days a week each person took aspirin. Lacking this information we ascertained coronary heart disease death rates in relation to aspirin use in terms of "never," "seldom," or "often." Presumably people who took aspirin daily or

nearly so would say that they took it often. Our results are inconsistent with the hypothesis that taking aspirin often results in reduced death rates from coronary heart disease.

Since this subject is important we are concerned lest our results be misleading. We will discuss some of the possible difficulties.

A major question is how often aspirin was taken by people who said that they took it often. An idea of this can be obtained by comparing our data with data collected by Dr. Jick and his associates.<sup>1</sup> In the Boston studies patients admitted for diseases likely to lead to heavy use of aspirin—for example, arthritis—were excluded from both subject and control groups.<sup>1</sup> Dr. Jick has kindly provided us with information showing that the proportion of daily aspirin users was greater among all patients than among those selected for the control group. A comparison of his data with ours suggests that somewhere between one-third and half of our subjects who said that they took aspirin often took it daily or nearly so. This would have a diluting effect on our results if it is true that only regular use of aspirin reduces coronary heart disease death rates.

What concerns us most is the possibility that frequent use of aspirin may not be a fixed habit even among people who have arthritis. Some of the subjects who were taking aspirin often at the time they enrolled in the study may have stopped doing so long before the end of the six-year period and vice versa. It seems reasonable to suppose, however, that such reversal of habits is less likely to occur in a short period of time than in a long period. Thus we made analyses confined to the early part of the study—the first 39 months, the first year after enrollment, and the first six months after enrollment. The results of these analyses did not alter the picture.

Cause of death was ascertained from information on death certificates, which is not always correct. This would tend to dilute the findings, but it seems unlikely that it would reverse the direction of the results. In the Boston study patients admitted to hospital for acute myocardial infarction were compared for use of aspirin with patients in hospital for other conditions. In our study death rates from coronary heart disease were examined with respect to use of aspirin. "Death due to coronary heart disease" is not synonymous with "acute myocardial infarction."

Having said all this we are still at a loss to explain why—if regular use of aspirin greatly reduces the risk of acute myocardial infarction—death rates from coronary heart disease were no lower among people who took aspirin often than among people who did not do so.

## References

- <sup>1</sup> Boston Collaborative Drug Surveillance Group, *British Medical Journal*, 1974, 1, 440.
- <sup>2</sup> Elwood, P. C., et al., *British Medical Journal*, 1974, 1, 436.
- <sup>3</sup> Hammond, E. C., *National Institute of Health Monograph*, 1966, 19, 127.
- <sup>4</sup> Hammond, E. C., and Garfinkel, L., *Archives of Environmental Health*, 1969, 19, 167.
- <sup>5</sup> Hammond, E. C., Garfinkel, L., and Seidman, H., *Circulation*, 1971, 43, 31.
- <sup>6</sup> Spain, D. M., and Bradess, V. A., *Chest*, 1970, 58, 107.