study[8] a clear and urgent case for further randomized controlled clinical trials is obvious.

This trial elicited an immense amount of goodwill and support from hospital physicians, general practitioners, and other medical and ancillary workers, to all of whom we express sincere thanks. The work also necessitated considerable help from colleagues in the M.R.C. Unit and in Nicholas Research Laboratories, to whom we are most grateful. We also thank Professor J. P. D. Graham of the Welsh National School of Medicine and colleagues in the M.R.C., D.H.S.S., and the Office of Population Censuses and Surveys who advised on the conduct of the trial after May 1972; the monitoring group (Professors Sir Richard Doll, F.R.S., Jerome Cornfield and D. D. Reid in addition to P.M.S.); and the nurses who handled the extended field work (Nurses L. Baker, E. R. Hill, S. P. Hill, T. Saunders, and W. Softley).

Requests for reprints to P.C.E.

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Regular Aspirin Intake and Acute Myocardial Infarction

BOSTON COLLABORATIVE DRUG SURVEILLANCE GROUP

British Medical Journal, 1974, 1, 440-443

Summary

The results of two large independent studies involving a combined total of 776 patients treated in hospital with a discharge diagnosis of acute myocardial infarction and 13,898 patients with other discharge diagnoses showed a negative association between regular aspirin intake and non-fatal myocardial infarction. The data are consistent with the hypothesis that aspirin protects against this disease. Clinical trials are needed to determine whether this hypothesis is correct.

Introduction

Since 1966 the Boston Collaborative Drug Surveillance Program has used nurses to carry out intensive monitoring of medical patients in several hospitals in four countries.[1] As part of the routine data collection, information has been obtained on drug intake before admission and on discharge diagnoses. For some time a strong negative association between regular aspirin intake before admission and a discharge diagnosis of acute myocardial infarction has been observed in these data (Study I). During the first ten months of 1972 a separate study was undertaken to obtain additional data on the relation of drug use to disease. This entailed a survey of drug exposure and discharge diagnoses in about 25,000 consecutive admissions to the medical and surgical wards of 24 hospitals in the Boston area.[2] The second study again showed a negative association between regular aspirin use and the development of acute myocardial infarction (Study II). Detailed analyses of both sets of data are presented here.

Subjects and Methods

STUDY I

Information on "regular" drug intake in the month before admission and on discharge diagnoses was collected in a standard fashion by nurse monitors in over 9,000 patients admitted to various medical wards in eight hospitals. On admission, patients were asked whether they took drugs regularly for a wide variety of indications (for example, contraception, pain, headache, etc.). Regular drug intake was defined as "regular use of the same medication on a scheduled basis" (in the case of aspirin intake the definition was generally interpreted as "daily" use). When such a history was given for any drug, the duration of consumption was recorded, but no effort was made to determine the dosage taken. Diagnoses were obtained from the attending physicians at the time of discharge.

This programme was not designed to test any particular hypothesis, but rather to evaluate relationships between a large variety of drugs and diseases. Thus, at the time of obtaining the data, no specific interest was directed towards either aspirin use or acute myocardial infarction.

For the purposes of the present evaluation of the relation between regular aspirin intake and acute myocardial infarction, patients receiving any preparation containing aspirin were combined to form an "aspirin-exposed" group. Certain patients were excluded from the final analyses. These were: (1) patients below the age of 40 and above the age of 69 years; (2) patients with *first* diagnoses which are likely to be associated with aspirin intake—namely, cancer, headache, any form of arthritis, any other musculoskeletal disorder, any form of gastrointestinal bleeding, alcoholism, and anxiety or any psychological disturbance. With these restrictions, the final analyses of data from Study I were based on a population of 325 patients with a discharge diagnosis of acute myocardial infarction and 3,807 controls.

Among the controls the discharge diagnosis was: 60% cardiovascular disease; 28% respiratory disease; 16% diabetes; 11% gastrointestinal disease; 10% renal disease; and 15% none of these diagnoses. The percentage frequency of regular aspirin use in these categories was 4·5, 5·1, 4·1, 5·5, 6·9, and 7·1, respectively. Angina pectoris or coronary insufficiency, or both, was a discharge diagnosis in 270 controls with cardiovascular disease. Among them the frequency of regular aspirin use was 4·4%.

STUDY II

Study II was based on a special multipurpose survey carried out from January to October 1972 in the general medical and

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See end of article for membership

surgical wards of 24 hospitals in the greater Boston area. Details of the methods used in this survey have been presented previously,[2] but several features require emphasis. Firstly, certain patients were not included in the survey—namely, those who had been in hospital during the three-month period immediately preceding the current admission, and those who were medically unfit for interview. In addition, an unknown fraction of patients in hospital for less than 72 hours were missed because they were discharged before they could be interviewed.

Secondly, all patients were interviewed shortly after admission by specially trained nurses. All were asked if they had regularly taken medications for any of a wide variety of indications (for example, diabetes, contraception, arthritis, headache, pain, etc.) during the previous three months. When a positive history was obtained, the duration of drug use and its frequency in terms of days per week was recorded. In addition, specific information concerning drug intake in the week before admission was obtained. Nevertheless, the exact dosage taken was not determined. For this evaluation a patient was considered to be a "regular" aspirin user if he gave a history of aspirin ingestion at least four days per week and if he continued to take aspirin during the week before admission.

Thirdly, limited information was routinely recorded on past medical histories. Patients were asked about previous myocardial infarction, diabetes mellitus, arthritis, hypertension, rheumatic fever, and peptic ulcer.

Finally, diagnoses at the time of discharge were recorded. The accuracy of the discharge diagnosis of acute myocardial infarction was checked by an experienced cardiologist (Dr. H. E. Thomas). Of the first 225 patients discharged with this diagnosis, 197 (88%) fulfilled the diagnostic criteria set by the World Health Organization.[3] Such accuracy was considered adequate for the purposes of this study.

For the final analyses of Study II, the same exclusion criteria were used as in Study I. In addition, 22 patients who entered hospital for other reasons but who suffered an acute myocardial infarction after the fourth hospital day were excluded. The analyses were thus based on a total of 451 patients with a discharge diagnosis of acute myocardial infarction and 10,091 controls.

Among the controls, the discharge diagnosis was as follows: 41% cardiovascular disease; 20% gastrointestinal disease; 14% respiratory disease; 10% diabetes mellitus; 8% renal disease; and 35% none of these diagnoses. The percentage frequency of regular aspirin use in these categories was 7·0, 7·0, 7·1, 7·7, 6·7, and 7·3, respectively. Among controls admitted to surgical wards the frequency of aspirin use was 6·9%, while among those admitted to medical wards it was 7·1%. Angina pectoris or coronary insufficiency, or both was a discharge diagnosis in 572 controls with cardiovascular disease. Among them the frequency of regular aspirin use was 7·0%.

Every effort was made to conceal any specific interest of this study from nurse monitors, patients, and attending physicians. Nevertheless, this effort may not have been entirely successful in the case of aspirin since awareness of an interest in this drug was present among the central staff responsible for training nurses. Furthermore, by the time this study began, statements about a possible preventive effect of aspirin on acute myocardial infarction had been made in both lay and scientific publications.[4] The influence of bias in the data collection, therefore, represents a potential problem in the interpretation of data from the second study.

Results

STUDY I

Among 325 patients with acute myocardial infarction, three (0·9%) gave a history of regular aspirin use before admission. Among 3,807 controls, 188 (4·9%) gave such a history. Thus the estimated crude risk ratio (R.R.) for acute myocardial infarction among those exposed to regular aspirin was 0·18 relative to those who were not. The frequencies of aspirin use among cases and controls by age and sex are given in table I and by hospital in table II. Control of these factors the estimates of summary risk ratio (S.R.R.) were 0·19 ($\chi^2_{(1)} = 9·11$; $P < 0·003$) and 0·21 ($\chi^2_{(1)} = 7·79$; $P < 0·006$), respectively.[5]

TABLE I—*Study I. Distributions of Cases of Acute Myocardial Infarction and Controls according to regular Aspirin Intake By Sex and Decade*

	Age		Aspirin users	Aspirin non-users	Total
Men	40-49	Cases	2 (3·8%)	50	52
		Controls	29 (4·3%)	643	672
	50-59	Cases	0 (0·0%)	86	86
		Controls	34 (4·1%)	797	831
	60-69	Cases	0 (0·0%)	112	112
		Controls	35 (4·4%)	769	804
Women	40-49	Cases	0 (0·0%)	8	8
		Controls	33 (8·0%)	378	411
	50-59	Cases	0 (0·0%)	33	23
		Controls	33 (6·2%)	496	529
	60-69	Cases	1 (2·3%)	43	44
		Controls	24 (4·3%)	536	560

S.R.R. (M.H.) = 0·19 $\chi^2_1 = 9·11$ $P < 0·003$.

TABLE II—*Study I. Distributions of Cases of Acute Myocardial Infarction and Controls according to regular Aspirin Use by Hospital*

Hospital	Aspirin users		Aspirin non-users	Total
1	Cases	0	2	2
	Controls	6 (4·6%)	125	131
2	Cases	0	35	35
	Controls	27 (4·7%)	553	580
3	Cases	0	20	20
	Controls	46 (5·7%)	756	802
4	Cases	0	68	68
	Controls	19 (3·0%)	620	639
5	Cases	0	34	34
	Controls	16 (4·4%)	346	362
6	Cases	0	30	30
	Controls	55 (8·2%)	613	668
7	Cases	1 (1·2%)	84	85
	Controls	7 (1·6%)	434	441
8	Cases	2 (3·9%)	49	51
	Controls	12 (6·5%)	172	184

S.R.R. (M.H.) = 0·21 $\chi^2_1 = 7·79$ $P < 0·006$.

The frequency of aspirin use among cases and controls with diabetes was 1/48 (2·1%) and 26/640 (4·1%), respectively; for cases and controls with hypertension it was 1/22 (4·5%) and 17/441 (3·9%), respectively, and for cases and controls with a *secondary* diagnosis of arthritis it was 0/19 and 19/136 (14·0%), respectively. Division of the patients according to smoking and coffee-drinking habits showed no material difference in aspirin intake among these subgroups.

Among the 188 controls who used aspirin, 52% consumed aspirin alone, 12% took buffered preparations, and 36% took compound preparations containing aspirin. Among the three cases using aspirin, two consumed it alone and one took a compound preparation.

Among the controls, 37% took aspirin for headache, 57% took it for "pain", and 6% took it for other reasons. Among the three cases using aspirin, two took it for headache and one for "pain".

STUDY II

Among 451 patients with acute MI, 16 (3·5%) gave a history of regular aspirin use before admission, whereas among 10,091 controls 702 (7·0%) gave such a history. Thus the estimate of crude R.R. for acute myocardial infarction among regular aspirin users was 0·49 relative to those who were not exposed. The frequencies of aspirin use among cases and controls by age, sex, and past history of myocardial infarction are given in table III. On control of these factors the S.R.R. estimate was 0·53; ($\chi^2_{(1)} = 5·2$, $P < 0·03$).

TABLE III—*Study II. Frequencies of regular Aspirin use among Infarct Cases and Controls by Age, Sex, and Past History of Myocardial Infarction (Percentages in Parentheses)*

		Myocardial Infarction Cases			Controls		
			Aspirin			Aspirin	
		Users	Non-users	Total	Users	Non-users	Total
No past History of Myocardial Infarction	Men						
	40-49	1 (1·9)	51	52	58 (4·7)	1,185	1,243
	50-59	2 (2·7)	71	73	60 (4·2)	1,353	1,413
	60-69	1 (1·2)	76	77	58 (4·8)	1,150	1,208
	Women						
	40-49	1 (7·7)	12	13	150 (7·6)	1,821	1,971
	50-59	1 (3·4)	28	29	146 (8·8)	1,511	1,657
	60-69	4 (8·0)	46	50	141 (9·9)	1,290	1,431
Past History of Myocardial Infarction	Men						
	40-49	0 (0·0)	22	22	6 (5·5)	103	109
	50-59	3 (5·1)	56	59	16 (5·5)	276	292
	60-69	1 (2·9)	34	35	18 (5·6)	304	322
	Women						
	40-49	0 (0·0)	3	3	7 (14·6)	41	48
	50-59	0 (0·0)	12	12	15 (10·9)	122	137
	60-69	2 (7·7)	24	26	27 (10·4)	233	260
	Total	16 (3·5)	435	451	702 (7·0)	9,389	10,091

S.R.R. (M.H.) = 0·53.
$\chi^2_1 = 5{\cdot}2$, $P < {\cdot}03$.

The frequencies of regular aspirin use among cases and controls with diabetes was 2/69 (2·9%) and 81/1049 (7·7%), respectively; for cases and controls with hypertension it was 0/39 and 67/831 (8·1%), respectively; for cases and controls with a past history of myocardial infarction it was 6/157 (3·8%) and 89/1168 (7·6%), respectively; and for cases and controls with a *secondary* diagnosis of arthritis it was 1/16 (6·3%) and 92/519 (17·7%), respectively.

Among the controls who used aspirin, 46% consumed it alone, 27% took a buffered preparation, and 26% took compound preparations containing aspirin. The distribution among cases was nine (56%) using it alone, five (31%) using buffered preparations, and two (13%) using compounds containing aspirin.

Among controls, 54% took aspirin for headache, 42% for pain, and 4% for other reasons. Among the cases, nine (56%) took it for headache, five (31%) for pain, and two (13%) for other reasons.

TABLE IV—*Study II. Distribution of Infarct Cases and Controls according to regular Aspirin Use. The Subjects have been stratified according to a multivariate Risk Score in the Range common to both Cases and Controls*

Risk Quintile[1] Among Cases		Regular Aspirin Use		
		Present	Absent	Estimate of R.R
1	Cases	4	86	0·55
	Controls	472	5,579	
2	Cases	2	86	0·45
	Controls	86	1,660	
3	Cases	2	87	0·40
	Controls	62	1,090	
4	Cases	2	87	0·32
	Controls	39	543	
5	Cases	6	85	0·88
	Controls	40	497	

Est (ML) of R.R. = 0·53
90% CL for R.R. = 0·33, 0·84
P value (two-sided) = ·02
[1]Myocardial infarction cases have been divided into five approximately equal strata. The first quintile represents the 20% of cases with the lowest risk scores, together with all control subjects in the range of that score. The second quintile represents 20% of cases with the next higher risk scores, together with all control subjects in the range of that score and so on.

MULTIVARIATE ANALYSIS

To control simultaneously several confounding factors and to explore further the negative association of aspirin use in terms of the risk for myocardial infarction, the data were submitted to a multivariate analysis.

A multivariate score, characterizing for each subject the individual risk for acute myocardial infarction was derived and employed.[2,6] The score involved sex; history of myocardial infarction; history of peptic ulcer; smoking (ex-smoker, current smoker, other); season (January to May, June to September); hospital (each of 24 hospitals); coffee and tea consumption (none, 1-5 cups/day, 6+ cups/day); histories of use of antianginal drugs (yes or no) and digitalis preparations (yes or no); diabetes and hypertension (yes or no—based on discharge diagnosis and history of use of antidiabetic drug); secondary diagnosis of arthritis (yes or no); and religion (Jewish or other). The score for each subject was taken to be the value of the linear discriminant function separating cases and controls. As expected, subjects with the lowest risk scores tended to be young, female, nonsmoking, etc., whereas those with the highest scores were particularly characterized by a history of coronary heart disease.

The data with stratification by the multivariate risk score are presented in table IV. Within the range of the score that was common to cases and controls there were 447 cases and 10,068 controls. From these data the summary estimate of the risk ratio was 0·53 with 90% two-sided confidence limits of 0·33 and 0·84, and a two-sided P value of 0·02. The risk ratios across the strata were consistent with uniformity of the underlying risk ratio.

Discussion

In view of the known effects of aspirin on the coagulation mechanisms, and perhaps most importantly on platelet aggregation,[7-9] it is reasonable to suggest that aspirin may offer some protection against the development of acute myocardial infarction. Indeed, the use of aspirin as a preventive measure has been advocated solely on the basis of laboratory findings.[4] The two studies described here show a negative association between regular aspirin ingestion and non-fatal infarction which is consistent with the hypothesis that it confers some degree of protection. Nevertheless, it is important to consider alternative explanations for the observed results, and to examine the other relevant data.

It is most unlikely that the negative association between aspirin and acute myocardial infarction occurred by chance since the statistical significance of the observed association is very high in the first study and even higher if the data from the two studies are combined. Of potential confounding factors that might explain the association, the present studies taken together eliminate age, sex, hospital, and the indication for use of aspirin. In addition, the association was present among diabetics, hypertensives, individuals with a *secondary* diagnosis of arthritis, and those with a past infarction. In Study II the simultaneous control of many risk factors for myocardial infarction by multivariate analysis did not materially influence the findings. (In Study I multivariate analysis was not employed since there were only three cases using aspirin.) On balance, it seems most unlikely that the association could have resulted from confounding by factors which were measured in these studies.

On the other hand, data on factors such as personality, diet, and exercise were not available for analysis and conceivably confounding by these factors is important. This possibility

could be explored partially in relation to the use of other (non-salicylate) analgesics: if the negative association with aspirin is indeed due to confounding, there should be a similar association between non-salicylate analgesics and acute myocardial infarction. Unfortunately, the data on other analgesics are sparse: in the two series combined, 1·2% of the cases with myocardial infarction (nine patients) gave a history of regular intake of propoxyphene or acetaminophen, or both, whereas among controls the frequency was 1·4%.

Possibly the association arose as a result of selective early mortality of patients with infarction who were regular aspirin users, since the current series are composed of people who survived their infarction long enough to enter hospital. Nevertheless, the data reported by Elwood *et al.* in the accompanying paper provide evidence against an excess mortality among aspirin users.[10]

SELECTION BIAS

The possibility of selection bias in the choice of controls for the present analyses must also be considered. The objective in selecting controls was to exclude people who were in hospital for diseases which are either positively or negatively associated with regular aspirin use, because aspirin is used (or contraindicated) in the treatment of these diseases, or because aspirin causes them. To achieve this objective all patients with a first diagnosis of any disease which on a priori grounds might be thought to be related to regular aspirin intake were excluded. A review of the data after these exclusions were made showed that the frequency of aspirin use was similar among a variety of common diagnostic categories including angina pectoris and coronary insufficiency. Thus we consider it likely that the control patients were admitted for conditions which are essentially unrelated to aspirin use. Nevertheless, it remains possible that patients who use aspirin regularly are predisposed to be admitted to hospital with a wide variety of diseases other than acute myocardial infarction. If so, aspirin use among the controls examined in these studies would be spuriously high. This conjecture, even if true, is unlikely to have affected the results of Study I. It could, however, have altered, to some degree, interpretation of the results in Study II.

The quality of the history of drug intake given by patients with myocardial infarction appeared to be comparable to that given by controls, as indicated by the data on drugs other than aspirin. For example, in Study II 5·0% of cases gave a history of regular use of drugs for "insomnia" before admission as compared with 4·7% of controls. Hence the low frequency of reported aspirin use among MI patients is unlikely to be due to a tendency of cases not to report actual aspirin use.

Certainly, the quality of history taking was not biased with regard to the hypothesis at issue in the first study, but may have been in the second, because when the first body of data was collected there was no such hypothesis.

While the problems involved in the accumulation, analysis, and interpretation of the data are complex and difficult to resolve fully, there remains good evidence that a negative association between regular aspirin intake and non-fatal myocardial infarction does exist both for those with a first infarction and those with a recurrent episode. Elucidation of whether the association is causal requires controlled clinical trials in man. One such study comparing 300 mg of aspirin daily versus placebo in men who have recently had an acute myocardial infarction is presented in the accompanying paper by Elwood *et al.*[10] While the results of that study are consistent with a protective effect of aspirin against cardiovascular death, they are by no means conclusive.

Hence the available data, while suggestive, fall far short of establishing that aspirin prevents myocardial infarction. Thus these data should not preclude the conduct of controlled trials on ethical grounds. Such trials are vital before the use of aspirin for preventing myocardial infarction can be recommended with complete confidence. Two multicentre clinical trials involving a comparison of aspirin and placebo in the secondary prevention of myocardial infarction are currently in progress—one in the United States as part of the Coronary Drug Project, and one in Germany and Austria, initiated by Dr. K. Breddin of Frankfurt University and sponsored by Bayer AG.

We hope the results of these extremely important studies will provide additional evidence for or against the hypothesis that regular aspirin intake is useful in the prevention of acute myocardial infarction.

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Hospitals in Massachusetts which participated in the survey reported in this publication as "Study II" are: Beth Israel Hospital, Beverly Hospital, Boston University Hospital, Boston Veterans Administration Hospital, Brockton Hospital, Cardinal Cushing Hospital, Emerson Hospital, Faulkner Hospital, Framingham Union Hospital, Lawrence Memorial Hospital, Leonard Morse Hospital, Malden Hospital, Marlboro Hospital, Mount Auburn Hospital, New England Medical Center Hospital, New England Memorial Hospital, Newton-Wellesley Hospital, Norwood Hospital, Quincy City Hospital, Salem Hospital, Sancta Maria Hospital, South Shore Hospital, Symmes Hospital, and Waltham Hospital.

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