Aspirin Myocardial Infarction Study:

Design, Methods, and Baseline Results

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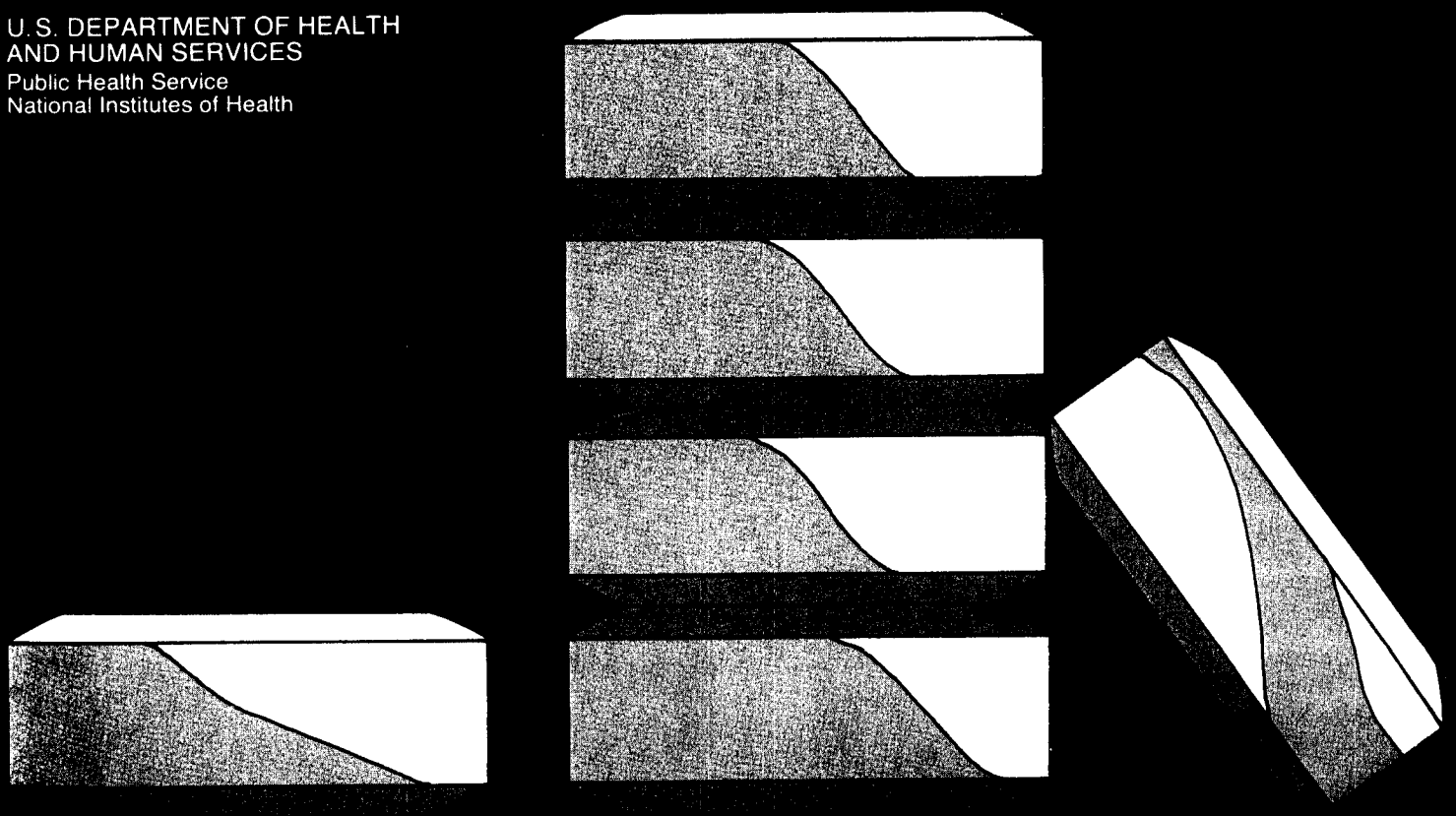

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ABSTRACT

The Aspirin Myocardial Infarction Study (AMIS), a cooperative clinical trial funded by the National Heart, Lung, and Blood Institute (NHLBI), was a randomized, double-blind study of the efficacy of aspirin (acetylsalicylic acid) in the secondary prevention of coronary heart disease. Four thousand five hundred and twenty-four men and women with documented evidence of previous myocardial infarction(s), recruited over a 1 year period by 30 Clinical Centers throughout the United States, were randomly assigned either to aspirin or placebo treatment group. Randomization occurred 8 weeks to 5 years (mean 2.1 years) following the qualifying myocardial infarction. Patients in the two treatment groups were monitored for the occurrence of fatal and nonfatal events for a minimum of 3 years.

INTRODUCTION

There is considerable evidence that platelet aggregation and platelet-induced thrombosis may play a role in several clinical events associated with coronary heart disease.[1] Aspirin can inhibit the formation of prostaglandin endoperoxides and thromboxane A_2, which aggregate platelets and induce vasospasm[2] but the clinical pharmacology of the drug is further complicated by recent findings that it also blocks the synthesis of prostacyclin (PGI_2),[3] an inhibitor of platelet aggregation and a vasodilator that is produced in blood vessels.[4]

Prior to 1975, preliminary evidence that regular administration of aspirin may be of benefit to patients with known coronary heart disease was published from several sources. The Boston Collaborative Drug Study[5] compared

the prevalence of aspirin use in hospitalized patients with a diagnosis of myocardial infarction to the prevalence in hospitalized patients with other diagnoses. These data showed a markedly lower use of aspirin in the myocardial infarction group relative to the other group. A study by Elwood, Cochrane, Burr, et al.,[6] compared in a prospective, randomized, double-blind manner, men with recent myocardial infarctions who were prescribed aspirin or placebo (300 mg per day). This trial showed an overall favorable, but not a statistically significant, effect of aspirin on mortality. The Coronary Drug Project Aspirin Study,[7] using 972 mg of aspirin per day, showed a 30 percent lower mortality in the aspirin treated group as compared with a placebo group. These results did not reach statistical significance. As a result of these encouraging but inconclusive findings, the Aspirin Myocardial Infarction Study (AMIS) was established.

STUDY DESIGN

The primary objective of the Aspirin Myocardial Infarction Study was to determine whether the daily administration of one gram of aspirin to men and women who had at least one documented myocardial infarction (MI) would result in a significant reduction in total mortality over a three year period. It was assumed that approximately 90 percent of the deaths in the study group would be due to cardiovascular causes. Secondary objectives were to evaluate the effects of aspirin in this group on the incidence of coronary heart disease (CHD) mortality, coronary incidence (CHD mortality and/or nonfatal myocardial infarction), fatal or nonfatal strokes, and intermittent cerebral ischemic attacks. Other objectives were to evaluate side or adverse effects of long-term aspirin therapy, to study the natural history of coronary heart disease by following patients in the placebo group, and to advance the methodology of long-term cooperative clinical trials.

While total mortality was the primary endpoint, cause-specific mortality and nonfatal endpoints, such as recurrent myocardial infarction, angina pectoris, peripheral arterial occlusion, pulmonary embolism, intermittent claudication, stroke, and intermittent cerebral ischemic attacks, were also monitored. For definitions of these endpoints see Appendix A.

Thirty Clinical Centers, a Coordinating Center, an Electrocardiogram Reading Center, a Central Laboratory, a Drug Distribution Center, and the NHLBI Project Office participated in the study (Appendix B). From October 1974 through May 1975, investigators from these units developed the study protocol, defined patient eligibility criteria, and designed the study forms.

A total daily dose of 1.0 gram of aspirin was selected based on the experience of a previous trial,[7] which suggested that this dose yielded favorable trends in mortality without producing excessive adverse effects. The study investigators recognized that although a lower daily dose would affect platelet aggregation, it was not known whether the observed beneficial effects were due to this platelet effect or to some other effect of aspirin.

The adoption of a twice daily dosage schedule was based on the desire to minimize the adherence problems inherent in a more frequent schedule. At the same time, the investigators wished to avoid the probability of increased side effects if a larger, single daily dose was used.

To be eligible for enrollment in AMIS, a person must have had a documented myocardial infarction on the basis of one of the following combinations of criteria:

1. Diagnostic Q wave(s) on a single ECG recording plus markedly elevated serum enzymes, plus typical or atypical symptoms.
2. Serial ECG recordings demonstrating evolution of ST-T changes indicative of transient ischemia plus markedly elevated serum

enzymes plus typical symptoms.

3. Diagnostic Q wave(s) plus serial ECG recordings demonstrating evolution of ST-T changes indicative of transient injury plus typical or atypical symptoms.
4. Serial ECG recordings demonstrating development of new diagnostic Q wave(s).

Appendix C lists the AMIS electrocardiographic criteria for diagnostic Q waves and ST-T changes. For the enzymes to be considered markedly elevated, at least two different serum enzymes had to exceed twice the upper limit of normal for the laboratory in which they were measured or the serum glutamic oxalacetic transaminase (SGOT) should exceed three times the upper limit of normal. These changes must have occurred within 72 hours of onset of symptoms, consistent with an acute myocardial infarction.

Patients were not enrolled until 8 weeks after a documented acute myocardial infarction. There was concern that death within 8 weeks of infarction would be due to factors not likely to be affected by aspirin. It was also thought that there was a potential for harm from aspirin while the infarcted tissue was organizing and scar tissue was forming. In the absence of reliable estimates of mortality, the investigators elected to exclude patients who were more than 5 years beyond the qualifying myocardial infarction.

An age limitation of 30 through 69 years was chosen. Those less than 30 were excluded because of the high likelihood of a different etiology for their cardiovascular disease.

Patients who had undergone previous surgery for coronary heart disease were excluded from enrollment because of the concern that the surgery might have altered the natural history of the disease.

Persons with a systolic blood pressure greater than 180 mm Hg or a diastolic blood pressure greater than 105 mm Hg, measured by an average of

three independent readings several weeks apart, were excluded. Uncontrolled hypertension was felt to be an important risk for mortality which would not be affected by aspirin; the possible additional risk from aspirin in cerebral hemorrhage was also a concern.

Patients taking drugs that in combination with aspirin might pose added risk to the patient (e.g., anticoagulants) were ineligible for enrollment. In addition, people on non-study aspirin, dipyridamole, or sulfinpyrazone were excluded; it was felt that these platelet-affecting drugs could reduce any observed difference in mortality due to study aspirin if the effect of aspirin was due to the platelet activity. Data were insufficient to warrant excluding people taking other drugs that modify platelet function.

Although there are no data suggesting that aspirin is teratogenic, for patient safety it was decided to exclude women capable of becoming pregnant. Excluding these women would have little impact on patient recruitment and a minimal amount of scientific information would be lost. Eligibility criteria are listed in Table 1.

A study sample size of 4,250 patients was determined based on the following:

A. The study would have one treatment (aspirin) group and one control (lactose placebo) group to which participants would be randomly assigned in equal proportions.

B. The primary endpoint would be total mortality; all individuals would be followed for a minimum of 3 years.

C. The study population would be composed of 85 percent men (with a 3 year mortality of 12.8 percent, as observed in the Coronary Drug Project placebo group[8]) and 15 percent women (with a mortality rate that is 88 percent of that in men[9]).

D. The ingestion of aspirin would effect a 30 percent reduction in mortality, compared to the placebo group.

E. A one-tailed test of significance would be performed with a 5 percent level of significance and 90 percent power. The one-tailed test of significance was chosen because aspirin has not been shown to have major toxicity and because previous studies had either shown a trend in favor of aspirin or, at worst, no difference.

F. Aspirin would yield a beneficial effect immediately.

G. Ninety percent of the patients in the aspirin group would take an effective dose of aspirin in the first year; 82 percent in the second year; and 74 percent in the third year.

H. Eight percent of the patients in the placebo group would take aspirin on a regular basis in the first year and continue to do so; an additional 8 percent in the second year; and an additional 8 percent in the third year.

I. All persons would be analyzed according to the treatment assignment at entry regardless of adherence to study drug.

STUDY ADMINISTRATION

The administration of the study was designed to enhance adherence to study protocol and to promote effective communication and cooperation among the various participating centers.

1. The Policy-Data Monitoring Board acted in a senior advisory capacity to NHLBI throughout the study by periodically reviewing performance of the participating centers, monitoring study results and evaluating the treatment for beneficial and adverse effects. This board met at least semiannually with quarterly review of data. All data re-

views were unblinded as to treatment group; none of the voting members of the board were involved in the operational aspects of the trial and no one attending board meetings examined study patients.

2. The Steering Committee provided scientific direction for the study at the operational level. It consisted of representatives chosen from the participating centers and met semiannually. Subcommittees established by the Steering Committee are listed in Appendix B.
3. The Technical Group, consisting of senior personnel from all the participating units, met semiannually. At these meetings decisions of the Steering Committee were reviewed and acted upon, the progress of the study was reviewed, and ideas for improving adherence to study protocol were discussed.

PATIENT RECRUITMENT

1. Initial Screening

Clinic and hospital records were reviewed in order to identify men and women, aged 30 to 69, who had at least one ECG-documented myocardial infarction. Beginning May 28, 1975, potentially eligible patients were invited to the AMIS Clinical Center for orientation to the study. If the patient was interested, his/her eligibility was further evaluated at Initial Visit 1 by means of a brief clinical history and a limited physical examination. An electrocardiogram, clinical information, and laboratory data, obtained from either hospital or clinic records, were used for documenting and dating the myocardial infarction. At this time, the patient was advised not to use non-study aspirin or aspirin-containing drugs. The patient was also given a supply of acetaminophen for

use as an analgesic or antipyretic in place of aspirin.

Through this process, 5,396 patients were identified as potentially eligible for enrollment at Initial Visit 1. Of these, 40.4 percent were identified from a review of hospital records; 34.5 percent were a result of self-referral from publicity campaigns and the others were from miscellaneous sources. Table 2 presents the source of referrals by treatment group. The differences between treatment groups were not greater than two standard errors.

A potentially eligible patient was asked to report for Initial Visit 2 approximately 3 weeks later. At this visit, a comprehensive review of the objectives and design of the study was conducted and known side effects of aspirin were discussed. A chest X-ray, evaluated at the Clinical Center, was performed and urine and blood specimens were obtained. The patient was again advised against the use of non-study aspirin during the course of the study. Initial Visit 2 was completed by 4,888 persons.

2. Enrollment

A patient who completed Initial Visit 2 was invited to report for a Baseline Visit approximately 5 weeks after Initial Visit 2 if the following three conditions were met:

A. The ECG Reading Center verified that the patient's qualifying ECG's and supporting data met the AMIS eligibility criteria for a definite myocardial infarction.

B. The Central Laboratory determination revealed no salicylates in the patient's urine collected at Initial Visit 2.

C. The Coordinating Center confirmed all of the patient eligibility criteria as reported on the Initial Visit Form (submitted after Initial Visit 2).

Once these conditions were met, the Coordinating Center assigned a coded bottle number to the patient and mailed a sealed treatment allocation envelope containing a coded bottle number to the Clinical Center. A separate randomization scheme was used for each Clinical Center. Treatment assignments were double-blind; neither the patient nor the Clinical Center physician was informed of the treatment identity. Four thousand seven hundred forty-five treatment allocations were issued. Each treatment allocation envelope contained the patient's identifiers, so that the envelope would be opened only for the specified patient. At the Baseline Visit, if the patient continued to meet the eligibility criteria, the patient was invited to participate in the trial. If the patient agreed and signed an informed consent form, a comprehensive, standard history was obtained, physical examination was performed, and resting ECG was taken.

At the completion of the Baseline Visit, the treatment allocation envelope was opened and the patient was assigned to a coded bottle of study medication. The opening of the envelope determined the patient's date of entry into the study. Each patient was directed to take one capsule of study medication twice a day. All capsules were identical in appearance and were sealed to discourage attempts at unblinding.

The patient was again reminded to avoid the use of non-study aspirin and aspirin-containing products during the course of the study and was given an additional supply of acetaminophen.

The first patient was randomized in July 1975 and the last in August 1976. During this period, 4,524 patients were enrolled in the study (Table 3); 221 treatment allocation envelopes were returned unopened because at baseline the patients were found to be

ineligible for enrollment into the study and, therefore, were not randomized.

PATIENT FOLLOWUP

All patients enrolled in AMIS were followed for at least 3 years and were asked to report to the Clinical Centers at 4 month intervals, with the exception of the first followup visit which was scheduled 1 month after entry into the study (Table 4).

At each followup visit, a hematocrit was performed at the Clinical Center and urine specimens were forwarded to the Central Laboratory for salicylate assays. Except for the visit 1 month after baseline, a test of platelet aggregation was performed by the Clinical Center. Results of this test were placed directly onto a magnetic tape and could only be interpreted at the Central Laboratory, thus maintaining the blindness of the Clinical Center personnel. The platelet aggregation test plus the urine salicylate determination were used to monitor adherence to the study regimens. To further evaluate adherence, during each 4 month followup period, the Coordinating Center designated a random sample of participants from each Clinical Center to submit a urine specimen for additional salicylate determinations between visits to the Clinical Center.

At the annual followup visits, platelet count, prothrombin time, partial thromboplastin time, and chest X-ray were obtained for local interpretation; a resting ECG was taken, which was read at the ECG Reading Center. In addition to the urine salicylate determination, serum potassium, serum uric acid, serum cholesterol, serum triglycerides, SGOT, BUN, alkaline phosphatase, total bilirubin, and fasting serum glucose were included as a basic part of the annual followup visits; these determinations were conducted at the Central Laboratory (Appendix D).

If it was determined that a new cardiovascular event had occurred since the last completed study visit, a Nonfatal Event Form and Hospitalization Form, if appropriate, were completed and forwarded to the Coordinating Center. All data were forwarded to the Coordinating Center on standard study forms (Appendix E).

If a patient failed to keep a scheduled appointment for a followup visit, the Clinical Center staff contacted the patient to reschedule the visit and encouraged the patient to continue his/her active participation in the study. The staff also regularly contacted those patients who had discontinued followup to ascertain vital status and to encourage active participation. These regular contacts helped the Clinical Center staff to learn when patients have died. For deceased patients, the Clinical Center obtained death certificates and information as to cause of death and circumstances surrounding the death. The information was reported on a standard form which was submitted to the Coordinating Center, and then reviewed by the Mortality Classification Subcommittee. This committee was blinded as to treatment group in order to assign cause and chronology of death. Reports of nonfatal cardiovascular events were reviewed by a Nonfatal Events Subcommittee, which classified the events, blinded by treatment group.

QUALITY CONTROL PROCEDURES

To assess and insure the quality of the data reported by each of the participating units, internal and external quality control procedures were implemented as follows:

1. Clinical Centers

   Each Principal Investigator was responsible for insuring that the data reported from his/her Clinical Center were of high quality. To aid this effort, quarterly reports, generated by the Coordinating

Center, included summary assessments of adherence of the patients to drug regimen, missed patient visits, accuracy in the completion of study forms, and timeliness of the submission of laboratory samples and ECGs. In addition, the Coordinating Center, Central Laboratory, and ECG Reading Center monitored the quality of data.

Periodically, fictional case histories were submitted to the Clinical Centers. The Clinical Center staff completed study forms based on the case histories and errors in form completion were discussed with the investigators at the semiannual meetings of the Technical Group.

2. ECG Reading Center

The ECG Reading Center monitored the quality of ECGs submitted by the Clinical Centers as well as the reliability of its own readings. On a monthly basis, linearity and time constant of the 30 Clinical Center ECG machines were evaluated; once a year, paper speed and frequency response were checked. If problems were detected, the Clinical Centers were notified and corrections were made. The ECG Reading Center also reviewed the quality of submitted study recordings and notified the Clinical Centers of any problems identified.

Each ECG at the ECG Reading Center was independently read by two coders. Discrepancies were adjudicated by the Principal Investigator of the center or his designate. In addition, a number of ECG's were reread to evaluate intra- and inter-coder variability.

3. Central Laboratory

The Central Laboratory maintained a high standard of quality control by monitoring its performance through daily calibration curves, normal and high control samples, and long-range drift control samples. If any of these measures indicated that a laboratory

test was beyond prespecified limits, that test was shut down until satisfactory control had been reestablished. For some analyses stability of control materials was monitored on a weekly basis by external analysis performed by a reference laboratory. In addition, specimens with known values were submitted in a blind fashion by the Clinical Centers. Results of these external surveillance samples were reviewed by the Quality Control Subcommittee.

The Central Laboratory monitored the performance of the Clinical Centers with regard to collection, storage, and shipment of serum and urine specimens and conduct of the platelet aggregation test. Performance reports were periodically sent to the Clinical Centers.

4. Coordinating Center

The quality control procedures implemented at the Coordinating Center focused on the patient adherence to the procedures stated in the protocol and accuracy and consistency of the data reported by the Clinical Centers.

Adherence, quality control, and Clinical Center performance reports were generated every 3 months. These reports included summary assessments of adherence of the patients to the drug regimen, missed patient visits, accuracy in the completion of study forms, and timeliness of the submission of laboratory samples and ECG's. These reports were reviewed by the Adherence and Quality Control Subcommittees and presented to the investigators at the semiannual meetings.

Data reported on the standardized study forms received from the Clinical Centers were reviewed for consistency. Forms with missing or discrepant data were returned to the Clinical Centers for appropriate corrections.

BASELINE CHARACTERISTICS

The data presented serve to describe the characteristics of the AMIS study group. These data were collected at the Initial Visits or at the Baseline Visit, prior to the initiation of the study treatment.

The average time from qualifying infarction to entry into the study was 25.0 months; 45.1 percent of the patients entered the study within 1 year to 3 years of the qualifying infarction; 16.2 percent entered between 6 and 12 months of the qualifying infarction; 12.1 percent of the patients entered within 6 months of the qualifying infarction (Table 5).

Prior to entry, 86.8 percent of the patients had only one diagnosed infarction while 11.6 percent of the patients had two infarctions. The average age at the time of the qualifying infarction was 52.7 years (Table 5).

Prior to enrollment in the study 66.4 percent of the patients were classified as Class I of the 1964 New York Heart Association Functional Classification; the remainder were Class II. (See Appendix F-1 for definitions.)

The cause of death for the father of the patient was reported as cardiovascular in 25.8 percent of the patients; 15.9 percent reported that the mother's death resulted from cardiovascular disease; 11.1 percent patients reported that the cause of death for both parents was cardiovascular disease (Table 5). A remaining 47.2 percent had parents still living or who had died from noncardiovascular causes.

As noted in Table 6, the mean age of the study group at entry was 54.8 years; the study group was comprised of 88.9 percent men and 11.1 percent women. Racial distribution of the study population was 91.6 percent white, 6.1 percent black, and 2.3 percent of other races. (See Appendix F-2 for definitions.)

Of the 4,524 patients, 85.6 percent were married; 54.0 percent of the patients were employed on a full-time basis. Heavy physical activity was

reported by 1.6 percent of the patients; 23.8 percent reported performing moderate physical activity; 56.6 percent reported light physical activity; and 18.0 percent were reported as having sedentary lifestyles. (See Appendix F-2 for definitions.)

Table 6 shows that 53.2 percent of the patients enrolled were former cigarette smokers. (See Appendix F-3 for definitions.) The study group contained 27.3 percent current cigarette smokers at baseline with an average of 7.9 cigarettes smoked per day. Cigars were smoked by 6.0 percent of the study group at baseline; 6.7 percent of the baseline group were pipe smokers.

More than 1.5 oz. of alcohol was reported consumed daily by 84.3 percent of the patients. (See Appendix F-3 for definitions.) Six or more cups of nondecaffeinated coffee per day was reported consumed by 14.8 percent of the patients; 2.1 percent of the patients reported consuming six or more cups of tea per day.

A history of angina pectoris at entry was reported by 31.6 percent of the study population; 24.2 percent reported arrhythmias documented by ECGs (Table 7). A history of diabetes mellitus was reported by 10.6 percent of the population; 10.0 percent reported heart failure.

Reported use of medications at entry into the study (Table 8) revealed that 37.5 percent of the patients were currently taking nitroglycerin or long-acting nitrates; 29.4 percent tranquilizers; 29.0 percent diuretics; 19.9 percent vitamins; 17.7 percent digitalis; and 12.1 percent propranolol.

An analysis of the reported use of aspirin-containing drugs prior to enrollment in the study (Table 8) revealed that 73.6 percent of the patients used aspirin-containing drugs less than once a month; 12.9 percent reported using aspirin-containing drugs at least one a month, but less than once a week; 7.6 percent reported using aspirin-containing drugs at least once a week, but less than once a day; and 6.0 percent reported using aspirin-containing

drugs at least once a day.

At entry, the mean pulse rate was 72.1 beats per minute (Table 9). The mean systolic and diastolic blood pressures, computed from mean of the readings collected at the two Initial Visits and at entry into the study, were 128.0 mm Hg and 79.9 mm Hg, respectively. The average body weight for males was 173.4 lbs; the average body weight for females was 142.8 lbs at entry.

The mean values of the laboratory determinations centrally analyzed at entry into the study are presented in Table 9.

The correlation matrix of the major coronary heart disease risk factors measured at entry is available upon request.

At randomization, 88 baseline variables were measured. Based on chance alone, four variables would have been expected to have a difference between the two treatment groups of two standard errors or greater. The following seven variables showed a difference of two standard errors:

1. History of heart failure
2. History of angina pectoris
3. History of ECG-documented arrhythmias
4. Use of digitalis
5. Use of nitroglycerin or long-acting nitrates
6. Use of propranolol (or other beta-blockers)
7. Use of other medications

All of these variables were more frequent in the aspirin group, however, several are interrelated. During evaluation of treatment effect for mortality or any of the other defined endpoints, these, as well as nonstatistically significant differences, are taken into account by using multivariate methods such as an analysis of covariance.

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TABLE 1

ELIGIBILITY CRITERIA

1. AGE GREATER THAN 29 OR LESS THAN 70
2. ECG-DOCUMENTED MYOCARDIAL INFARCTION 8 WEEKS TO 60 MONTHS PRIOR TO RANDOMIZATION
3. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS I OR II (1964)
4. NO PREVIOUS SURGERY FOR CORONARY HEART DISEASE, INSERTION OF PERMANENT CARDIAC PACEMAKER, OR PROSTHETIC HEART VALVE
5. NO LIFE-LIMITING DISEASE OTHER THAN CORONARY HEART DISEASE
6. NO CURRENT USE OF ASPIRIN OR ASPIRIN-CONTAINING DRUGS, ANTI-COAGULANTS, SULFINPYRAZONE OR DIPYRIDAMOLE
7. NO HISTORY OF ASPIRIN INTOLERANCE
8. NO HISTORY OF RECENT ULCER OR HISTORY OF BLEEDING DUE TO ULCER
9. WOMEN INCAPABLE OF BECOMING PREGNANT
10. WILLINGNESS TO PARTICIPATE IN STUDY

TABLE 2

PERCENT OF PATIENT REFERRALS BY TREATMENT GROUP AND SOURCE OF REFERRAL

SOURCE OF REFERRAL	TREATMENT GROUP ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
Private physician referral	8.2	7.7	7.9
Project physician referral	9.2	7.5	8.3
Self-referral	34.5	34.6	34.5
Hospital records	39.6	41.1	40.4
Other	8.6	9.1	8.8

*Aspirin-placebo difference greater than 2 standard errors.

**Aspirin-placebo difference greater than 3 standard errors.

TABLE 3

PERCENT OF BASELINE VISITS BY MONTH
AND TREATMENT GROUP

MONTH OF BASELINE VISIT	TREATMENT GROUP ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
July 1975	1.2	1.3	1.3
August 1975	3.4	3.6	3.5
September 1975	6.0	5.7	5.9
October 1975	7.5	6.8	7.1
November 1975	4.6	5.5	5.1
December 1975	7.3	6.7	7.0
January 1976	6.3	7.1	6.7
February 1976	6.0	5.8	5.9
March 1976	9.2	9.6	9.4
April 1976	10.8	10.9	10.9
May 1976	9.2	9.1	9.1
June 1976	13.2	13.2	13.2
July 1976	12.9	12.6	12.8
August 1976	2.3	2.0	2.2
Total	100.0	100.0	100.0

TABLE 4

DESCRIPTION OF PATIENT VISITS

	INITIAL VISIT 1	INITIAL VISIT 2	BASELINE VISIT	FOLLOWUP VISIT 1[1]	NONANNUAL FOLLOWUP VISITS[2]	ANNUAL FOLLOWUP VISITS[3]
Clinical Procedures						
Orientation to study	X	X	X			
Consent form			X			
Clinical history	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X
Advise against use of aspirin	X	X	X	X	X	X
Supply pt. with acetaminophen	X	X	X	X	X	X
Laboratory Tests						
a. Local Tests						
Hematocrit		X	X	X	X	X
Platelet aggregation test			X		X	X
Platelet count		X				X
Prothrombin time		X				X
Partial thromboplastin time		X				X
White blood cell count		X				X
Urinalysis			X	X	X	X
b. Central Tests						
Urine salicylate		X	X	X	X	X
BUN/SGOT/Bilirubin/ Alkaline phosphatase/ Cholesterol/Triglycerides/ Uric acid/Potassium/ Fasting glucose			X			X
1 hour glucose challenge			X			
ECG			X			X
Chest X-ray		X				X

[1]The first followup visit was scheduled 1 month after the patient's entry into the study.

[2]The nonannual followup visits were scheduled at 4, 8, 16, 20, 28, and 32 months after entry.

[3]The annual followup visits were scheduled at 12, 24, and 36 months after entry.

TABLE 5

DISTRIBUTION OF BASELINE CHARACTERISTICS,
BY TREATMENT GROUP

CORONARY HEART DISEASE INDICATORS	PERCENT OF PATIENTS IN ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
Time Since Qualifying Infarction			
< 6 months	12.8	11.3	12.1
≥ 6 months - 1 year	15.7	16.7	16.2
≥ 1 year - 3 years	44.4	45.9	45.1
≥ 3 years - 5 years	27.1	26.1	26.6
Mean (months)	25.1	25.0	25.0
Number of Myocardial Infarctions			
1	86.6	86.9	86.8
2	11.9	11.2	11.6
≥ 3	1.4	1.9	1.6
Mean	1.2	1.2	1.2
Age at Most Recent (Qualifying) Myocardial Infarction			
< 30	0.1	0.2	0.2
30-39	6.5	5.2	5.9
40-49	26.7	27.6	27.2
50-59	44.0	45.0	44.5
60-69	22.6	21.9	22.3
Mean	52.7	52.7	52.7
Age at Time of First Myocardial Infarction			
< 30	0.2	0.3	0.3
30-39	6.8	5.6	6.2
40-49	28.1	28.8	28.4
50-59	43.8	44.5	44.2
60-69	21.1	20.8	20.9
Mean	52.3	52.4	52.3
New York Heart Association Classification†			
Class I	65.8	67.1	66.4
Class II	34.2	32.9	33.6
Parental Death From CV Disease			
Father only	24.8	26.7	25.8
Mother only	15.8	15.9	15.9
Both parents	11.4	10.9	11.1
Neither parent[1]	48.0	46.4	47.2

†See Appendix F-1 for definitions of classes.

[1]Both parents died from noncardiovascular cause or parents are still alive.

*Aspirin-placebo difference greater than 2 standard errors.

**Aspirin-placebo difference greater than 3 standard errors.

TABLE 6

DISTRIBUTION OF BASELINE SOCIODEMOGRAPHIC CHARACTERISTICS, BY TREATMENT GROUP

SOCIODEMIOGRAPHIC CHARACTERISTICS	PERCENT OF PATIENTS IN ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
Age			
30-39	4.1	3.6	3.8
40-49	20.7	20.6	20.6
50-59	44.5	45.7	45.1
60-69	30.7	30.2	30.4
Mean	54.8	54.8	54.8
Sex			
Male	88.4	89.4	88.9
Female	11.6	10.6	11.1
Race*			
White	91.7	91.5	91.6
Black	6.3	5.9	6.1
Other	2.0	2.6	2.3
Marital Status			
Never married	4.5	4.6	4.5
Married	84.3	86.8	85.6
Divorced	5.2	4.5	4.8
Widowed	4.2	3.0	3.6
Separated	1.8	1.1	1.5
Work Status			
Full-time	53.0	55.1	54.0
Part-time	7.9	8.5	8.2
Not working	39.1	36.5	37.8
Lifestyle*			
Heavy physical activity	1.9	1.4	1.6
Moderate physical activity	23.1	24.5	23.8
Light physical activity	56.7	56.5	56.6
Sedentary	18.4	17.6	18.0

*See Appendix F-2 for definitions of race and life style classes.

*Aspirin-placebo difference greater than 2 standard errors.

**Aspirin-placebo difference greater than 3 standard errors.

TABLE 6 (Continued)

DISTRIBUTION OF BASELINE SOCIODEMOGRAPHIC CHARACTERISTICS, BY TREATMENT GROUP

SOCIODEMIOGRAPHIC CHARACTERISTICS	PERCENT OF PATIENTS IN ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
Cigarette Smoking History†			
Nonsmoker	19.7	19.2	19.5
Former smoker	52.8	53.6	53.2
Current smoker	27.5	27.2	27.3
Number of Cigarettes Smoked By Current Smokers			
≤ 5	71.5	71.4	71.4
6-15	9.4	8.6	9.0
16-25	11.8	12.4	12.1
26-35	3.6	3.5	3.5
36-45	2.5	3.2	2.9
> 45	1.2	0.9	1.0
Mean Number of Cigarettes	7.8	8.0	7.9
Cigar Smoking History			
Nonsmoker	77.8	77.4	77.6
Former smoker	16.1	16.7	16.4
Current smoker	6.1	5.9	6.0
Pipe Smoking History			
Nonsmoker	73.4	73.9	73.6
Former smoker	19.8	19.5	19.7
Current smoker	6.8	6.6	6.7
Amount of Alcohol Consumed Per Day†			
< 1.5 oz.	15.9	15.4	15.7
≥ 1.5 oz.	84.1	84.6	84.3
Amount of Non-decaffeinated Coffee Consumed Per Day			
< 6 cups	85.5	84.8	85.2
≥ 6 cups	14.5	15.2	14.8
Amount of Tea Consumed Per Day			
< 6 cups	98.0	97.7	97.9
≥ 6 cups	2.0	2.3	2.1

†See Appendix F-3 for definitions.

*Aspirin-placebo difference greater than 2 standard errors.

**Aspirin-placebo difference greater than 3 standard errors.

TABLE 7

PERCENT OF PATIENTS WITH MEDICAL EVENTS AT ENTRY,
BY TREATMENT GROUP

BASELINE HISTORY	TREATMENT GROUP ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
A. Medical History			
Stroke	1.1	1.7	1.4
Pulmonary embolism	0.8	0.8	0.8
Peripheral arterial occlusion	0.9	0.8	0.8
Heart failure	11.2*	8.9	10.0
Coronary arteriography	9.4	8.5	9.0
Angina pectoris	33.4*	29.8	31.6
ECG documented arrhythmia	25.5*	22.9	24.2
Cerebral ischemic attacks	2.0	1.9	1.9
Intermittent claudication	6.5	6.3	6.4
Diabetes mellitus	10.1	11.2	10.6
Bronchial asthma	1.4	1.3	1.3
Rheumatic heart disease	0.4	0.4	0.4
Lower GI disorder	1.4	1.6	1.5
Renal disease	5.2	5.0	5.1
Hepatobiliary disease	5.2	4.7	5.0
Symptomatic gout	5.1	4.4	4.8
Malignant neoplasm	1.8	1.9	1.9
Peripheral edema	1.8	1.2	1.5
Ventricular diastolic gallop	1.4	1.9	1.6
Basilar rales	2.0	1.6	1.8
Epigastric tenderness	0.4	0.2	0.3
Hepatomegaly	1.6	1.5	1.5
Splenomegaly	0.2	0.2	0.2

*Aspirin-placebo difference greater than 2 standard errors.

**Aspirin-placebo difference greater than 3 standard errors.

TABLE 8

PERCENT OF PATIENTS USING MEDICATIONS AT ENTRY,
BY TREATMENT GROUP

USE OF MEDICATIONS	TREATMENT GROUP ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
Antacids	5.2	5.1	5.2
Anticholinergics	0.9	1.2	1.1
Insulin	2.0	2.3	2.2
Oral hypoglycemic agents	2.6	3.1	2.8
Digitalis	19.5**	16.0	17.7
Antiarrhythmic agents	10.5	8.8	9.6
Antihypertensives other than diuretics	10.3	9.8	10.1
Nitroglycerin or long-acting nitrates	39.4*	35.6	37.5
Gout medication other than probenecid	3.5	2.9	3.2
Probenecid	1.1	0.8	0.9
Lipid-lowering drugs	5.0	4.6	4.8
Phenylbutazone	0.4	0.1	0.3
Indomethacin	0.8	0.8	0.8
Phenothiazines	0.6	0.7	0.7
Tricylic antidepressants	0.7	1.1	0.9
Antihistamines	3.4	3.0	3.2
Propranolol (or other beta-blockers)	13.1*	11.0	12.1
Corticosteroid preparations	0.7	0.4	0.5
Tranquilizers	30.1	28.8	29.4
Hypnotics, sedatives, barbiturates	6.6	7.1	6.9
Vitamins	19.9	19.9	19.9
Estrogen	1.9	1.6	1.8
Other drugs	16.3*	14.1	15.2
Diuretics	29.6	28.4	29.0
Aspirin-Containing Drugs Prior to Entry			
Less than once a month	73.0	74.2	73.6
At least once a month but less than once a week	12.4	13.4	12.9
At least once a week but less than once a day	8.1	7.0	7.6
At least once a day	6.6	5.4	6.0

*Aspirin-placebo difference greater than 2 standard errors.

**Aspirin-placebo difference greater than 3 standard errors.

TABLE 9

SELECTED CLINICAL, LABORATORY, ECG, AND X-RAY FINDINGS, BY TREATMENT GROUP

	TREATMENT GROUP ASPIRIN (N=2267)	PLACEBO (N=2257)	TOTAL
A. Mean Value			
Clinical Findings			
Pulse rate (beats per minute)	71.6	72.7	72.1
Blood pressure			
Systolic (mm Hg)	127.9	128.2	128.0
Diastolic (mm Hg)	79.6	80.1	79.9
Body weight			
Male (lbs)	173.4	173.1	173.4
Female (lbs)	142.6	142.8	142.8
Laboratory Findings			
Cholesterol (μ mole/L)	237.30	237.42	237.36
Triglycerides (m mole/L)	6.41	6.26	6.33
Uric acid (m mole/L)	6.20	6.19	6.20
Fasting glucose (m mole/L)	97.57	98.85	98.21
Potassium (m mole/L)	4.20	4.20	4.20
Alkaline phosphatase (μ/L-30°)	63.72	64.29	64.00
Urea (m mole/L)	16.67	16.70	16.68
Total bilirubin (μ mole/L)	0.65	0.66	0.66
SGOT (U/L-30°)	31.30	31.78	31.54
B. Percent of Patients			
ECG Findings			
Heart rate $\geq$ 70	40.6	43.7	42.1
Q/QS waves	80.1	81.1	80.6
ST depression	25.3	25.3	25.3
ST elevation	18.3	19.0	18.7
T wave abnormalities	67.8	66.4	67.1
Frequent VPB	3.5	4.0	3.8
Ventricular conduction defects	4.1	3.3	3.9
A-V conduction defects	3.4	2.9	3.2
X-ray Findings			
Cardiomegaly	9.5	8.7	9.1

APPENDIX A

DEFINITIONS OF NONFATAL EVENTS

1. Myocardial Infarction, Angina Pectoris

   a. Definition of Definite MI

      The patient was defined as having had a definite recurrent MI on the basis of at least one of the following sets of criteria:

      i. ECG recording(s) demonstrating development of new diagnostic Q wave(s).

      ii. Serial ECG recordings demonstrating evolution of ST-T changes indicative of transient ischemia or injury plus markedly elevated serum enzymes* plus typical symptoms.

   b. Definition of Probable MI

      The patient was defined as having had a probable recurrent MI on the basis of the following sets of criteria:

      i. Serial ECG recordings demonstrating evolution of ST-T changes indicative of transient ischemia or injury plus moderately elevated serum enzymes† plus typical or atypical symptoms.

      ii. Typical symptoms plus markedly elevated serum enzymes plus non-diagnostic ECG changes.

   c. Definition of Suspect MI

      The diagnosis of suspect MI was made if a myocardial infarction was thought to have occurred, but the AMIS criteria for Definite or Probable Myocardial Infarctions were not met. (For example, if a

*Markedly elevated serum enzymes: At least two different serum enzymes exceeding twice the upper limit of normal or SGOT exceeding three times the upper limit of normal.

†Moderately elevated serum enzymes: At least two different serum enzymes exceeding the upper limit of normal or SGOT exceeding two times the upper limit of normal (but less than three times the upper limit).

patient came under medical attention more than 72 hours after the onset of symptoms and there was no development of new diagnostic Q waves(s).)

d. New Event of Angina Pectoris Not Requiring Hospitalization

A new event of angina pectoris could only occur in a patient who had never previously experienced angina pectoris.

This diagnosis was made when there were episodes of pain, cardiac in origin (i.e., aching, tightness or pressure which might or might not radiate to the neck, jaw, shoulder or arm). The discomfort might commonly be associated with a history of occurrence in relation to effort with relief by rest in less than 10 minutes, and/or relief by nitroglycerin in less than 5 minutes. Typically, there were no significant ST-T changes or enzyme changes. The diagnosis of angina pectoris might also be made in the presence of atypical chest pain, when a stress test such as a treadmill test or atrial pacing had been performed and found to be positive.

e. Other Chest Pain of Cardiac Origin Requiring Hospitalization

This category included syndromes that did not have well defined criteria and frequently overlapped, but were not considered to be a myocardial infarction. These might include classical angina pectoris (new or recurrent) or syndromes such as unstable angina, coronary insufficiency, accelerating angina, pre-infarction angina, intermediate syndrome, or Prinzmetal's variant angina requiring hospitalization.

2. Stroke

A definite stroke was one in which objective neurologic deficits (motor weakness, speech defect, amaurosis or field defect, sensory symp-

toms) were observed for more than 3 weeks and were documented by a physician (i.e., observed by a study physician or recorded in the patient's medical records).

A probable stroke was one in which:

a) Objective neurologic deficits (drop attacks or gait disturbance, alteration of consciousness, vertigo or disequalibrium, bilateral blurred vision or diplopia) persisted for more than 3 weeks and were documented by a physician. or

b) Any of the above mentioned objective neurologic deficits persisted for more than 24 hours but less than 3 weeks ("reversible ischemic neurologic deficit").

A suspect but unconfirmed stroke was one in which objective neurologic findings persisting for more than 24 hours were reported but could not be confirmed. (Study physician did not observe the symptoms or hospital records were not available.)

3. Intermittent Cerebral Ischemic Attack

The diagnosis of definite intermittent cerebral ischemic attacks was made if in the judgment of the physician motor weakness, speech defect, or amaurosis or field defect occurred. The diagnosis of probable intermittent cerebral ischemic attack was made if, in the judgment of the physician, either sensory symptoms or drop attack or gait disturbance occurred.

The diagnosis of suspect intermittent cerebral ischemic attacks was made if alteration of consciousness, vertigo or disequalibrium, or or bilateral blurred vision or diplopia occurred or if for any other reason it was felt that an ICIA might have occurred, but a diagnosis of definite or probable ICIA could not be made.

4. Peripheral Arterial Occlusion

The diagnosis of definite peripheral arterial occlusion was made if the diagnosis was confirmed by angiographic or surgical findings.

The diagnosis of probable peripheral occlusion was made if both of the following criteria were met:

A. Symptoms of acute ischemia of any of the upper or lower extremities.

B. Absences of arterial pulsations in the corresponding limb or diminished arterial pulses with one or more of the following: pallor, muscular weakness, dependent rubor, prolonged return of color and venous filling after elevation, presence of ischemic ulcers or gangrene.

If symptoms of peripheral arterial occlusion were present but the above criteria were not met, the diagnosis of suspect peripheral arterial occlusion was made.

5. Intermittent Claudication

Leg pain was diagnosed as definite intermittent claudication when it possessed all of the following characteristics:

A. Included one or both calves.

B. Provoked by walking.

C. Never started at rest.

D. Made the patient either stop or slacken pace.

E. In a majority of occasions, disappeared in 10 minutes or less from the time when the patient stood still and reappeared if the same pace was resumed.

F. Absence of peripheral pulses in the affected limb(s).

The diagnosis of probable intermittent claudication was made if characteristics A through E were present but criteria F was not met.

The diagnosis of suspect intermittent claudication was made if characteristics B through E were present and leg pain was present in one or both thighs but not the calves.

6. Pulmonary Embolism

A diagnosis of definite nonfatal pulmonary embolism was made based on:

A. Diagnostic pulmonary angiogram, or

B. Perfusion scan showing segmental or lobar defect(s)

plus

1. PaO_2 below 90 mm Hg and $PaCO_2$ below 40 mm Hg,

and

2. Absence of congestive heart failure, pre-existing airway disease, and pneumonia,

and

3. A chest x-ray with no abnormality in the area abnormal on scan.

The diagnosis of probable nonfatal pulmonary embolism required any of the following combinations:

A. If blood gases were determined:

PaO_2 below 90 mm Hg and $PaCO_2$ below 40 mm Hg plus either

1. ECG evidence of newly developed right heart strain as evidence by S_1, Q_3, T_3 pattern or right axis deviation or right ventricular hypertrophy or incomplete right bundle branch block.

or

2. Two of the following:

   a. Hemoptysis.

   b. Pleuritic chest pain in a location not substernal or pleural friction rub.

   c. Phlebitis of lower extremity.

   d. One of the following radiographic abnormalities: infiltrate, effusion, elevated hemidiaphragm.*

B. If blood gases were not determined or if the patient was given O_2 and $PaO_2 \geq 90$ mm Hg:

Perfusion scan showing segmental or lobar defect(s) plus absence of congestive heart failure, pre-existing airway disease, and pneumonia and a chest x-ray with no abnormality in the area abnormal on the scan plus either

1. ECG evidence of newly developed right heart strain as evidenced by S_1, Q_3, T_3 pattern or right axis deviation or right ventricular hypertrophy or incomplete right bundle branch block.

or

2. Two of the following:

   a. Hemoptysis.

   b. Pleuritic chest pain in a location not substernal or pleural frication rub.

   c. Phlebitis of lower extremity.

The diagnosis of suspect nonfatal pulmonary embolism was made in all other cases where a pulmonary embolism was thought to have occurred but the above criteria were not met.

*The diagnosis of pneumonia had to be excluded.

APPENDIX B

PARTICIPATING UNITS

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Nancy H. Doub, Ph.D., Investigator
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Genell L. Knatterud, Ph.D., Statistician
Patricia Wilkins, Programmer
Jane Hagley, Coordinator
Dorothy Harris, Coordinator

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Pantel Vokonas, M.D.
Gary Wilner, M.D.

STEERING SUBCOMMITTEES

A. Editorial Review Committee: The Editorial Review Committee reviewed every scientific paper using unpublished AMIS data (including ancillary studies) that had been prepared for presentation and publication, as well as every paper or presentation using published AMIS data that purported to represent official AMIS views or policy.

James Schoenberger, M.D., Chairman
Nemat Borhani, M.D.
Lawrence Friedman, M.D.
Richard Hutchinson, M.D.
Christian Klimt, M.D., Dr.P.H.

B. Mortality Classification Committee: The Mortality Classification Committee reviewed all information concerning deaths of AMIS patients and coded cause of death for each decedent.

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Sidney Goldstein, M.D.
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Rafael Sobrino, M.D.

C. Publicity and Recruitment Committee: During the Recruitment Phase, this committee made recommendations regarding methods of patient recruitment, including the use of public media.

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William Bernstein, M.D.
Nemat Borhani, M.D.
Curt Furberg, M.D.
J. Joanne Hoover, M.D.
William F. Krol, Ph.D.
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D. Adherence Committee: This committee reviewed methods of monitoring and maintaining good patient adherence to study protocol and advised Clinical Centers of these methods.

William Bernstein, M.D., Chairman
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Curt Furberg, M.D.
Genell Knatterud, Ph.D.
Susan Pace, R.N.
Basil Williams, M.D.
Steven Zifferblatt, Ph.D.

E. Bibliography Committee: This committee was responsible for creating and maintaining a current bibliography on aspirin as it related to platelet function and coronary heart disease. Acetaminophen toxicity was also referenced.

Marvin Segal, M.D., Chairman
Ralph Fenderson, M.D.
William Friedewald, M.D.
Lawrence Friedman, M.D.
Bernard Lewis, M.D.
J. Judson McNamara, M.D.
Pantel S. Vokonas, M.D.

F. Quality Control Committee: This committee monitored the performance of the Clinical Centers, the Central Laboratory, the ECG Center, and the Coordinating Center. Reports prepared by this committee were presented to the Steering Committee and forwarded to the Policy-Data Monitoring Board and to the NHLBI Project Office. Information which would lead to unblinding of the study results was not reviewed by this committee.

William Friedewald, M.D., Chairman
Barbara DuBow (Deceased)
William F. Krol, Ph.D.
Dayton Miller, Ph.D.
Jorge Rios, M.D.
Gary Wilner, M.D.

G. Ancillary Studies Committee: This committee reviewed and made recommendations to the Steering Committee regarding all proposed ancillary studies.

Charles Laubach, Jr., M.D., Chairman
David Bayse, Ph.D.
Nancy Doub, Ph.D.
Lawrence Friedman, M.D.
Bernard Lewis, M.D.

H. Nonfatal Events Committee: This committee reviewed all information concerning specified nonfatal events.

Jorge C. Rios, M.D., Chairman
Allan H. Barker, M.D.
Curt Furberg, M.D.
Paul J. Geller, M.D.
Kenneth Hyatt, M.D. (Former)
William F. Krol, Ph.D.
Charles Laubach, Jr., M.D.
David Richardson, M.D.
Stephen Scheidt, M.D.

APPENDIX C

QUALIFYING ECG CRITERIA

The ECG Reading Center coded each electrocardiogram that was submitted in order to document the qualifying myocardial infarction. As seen in the following listing, each electrocardiogram was coded as to age and site of myocardial infarction, presence and site of injury, and presence and site of ischemia. This coding was used in documenting the presence of a myocardial infarction.

Myocardial Infarction

A. Age (Code for all locations) If no infarction was present

- Old: Diagnostic QRS abnormality, isoelectric ST segment and normal T vector
- Age Undetermined: Diagnostic QRS abnormality and a) ST segment elevation greater than 0.1 mV in corresponding anatomical area or b) T wave inversion in corresponding anatomical area. No previous ECG available for comparison.
- Acute or Evolving: a) New diagnostic Q abnormalities accompanied by either ST elevation greater than 0.1 mV or T wave inversion in same anatomical area. b) Evolution of electrocardiographic findings as demonstrated by:
    - Regression of ST or T in serial ECG observed in a 12-week period.
    - Appearance of these ECG abnormalities when compared to ECG recorded prior to the qualifying event (if available) or to most recent ECG for diagnosis of new events.

B. Criteria for Localization

Anteroseptal

- None present
- Q greater than 0.03 sec and Q/R ration 20% or greater in any of leads, V1-V3
- QS-V1 and QR-V2-V3
- QRS, QR or RS in leads V1-V4 with greater than 0.03 sec
- QS deflection V1-V3
- Initial R V1-V3 less than 0.02 sec and less than 0.1 mV amplitude, in the absence of left ventricular hypertrophy

Anterior

- None present
- A 0.03 sec Q wave in leads V2-V3 or V4 in the presence of a normal initial R wave in V1 and Q/R ratio greater than 25%; a normal septal Q is present in leads I, V5, V6
- A QS pattern in leads V2, V3 and normal initial R wave in V1

Anterolateral

- None present
- A Q wave greater than 0.03 sec and Q/R ratio greater than 25% in any of leads I, AVL, V5, V6

Localized (strictly) lateral infarction

- None present
- Q duration greater than or equal to 0.04 sec and Q/R ratio greater than 50% in lead AVL
- Q lead I, greater than 0.04 sec duration and Q/R ratio greater than 10%
- QS lead I or AVL
- Q I or AVL greater than or equal to 0.03 sec

Extensive Anterior Myocardial Infarction

- None present
- QS complex leads I, AVL, V1 through V6
- QS complex V1-V4 and Q duration in any combination of leads I, AVL, V5, V6 greater than 0.03 sec
- QS complex leads V1-V4 and R/S ratio V5-V6 less than 1 if QRS axis less than 315 degrees

Inferior (diaphragmatic) Infarction

- None present
- Q wave lead III greater than or equal to 0.02 sec and Q/R ratio greater than 20% with Q AVF greater than 0.1 mV or Q duration greater than 0.03 sec
- Q AVF greater than or equal to 0.03 sec
- Any Q wave lead III-AVF in the presence of a mean frontal QRS axis less than 30 degrees
- An R amplitude III, AVF, less than 0.1 mV in the presence of a mean frontal QRS axis less than 30 degrees
- QS complex leads III and AVF

Posterior Infarction

- None present
- R in leads V1 or V2 greater than 0.04 sec and R/S V1 greater than 1 in the absence of right ventricular conduction defect

Inferoposterior

- None present
- Combination of any inferior and posterior myocardial infarction
- Inferior myocardial infarction (as per above criteria and RSR' V1 with QRS duration less than 0.10 sec

Inferolateral

- None present
- Combination of inferior myocardial infarction (as per above criteria) and Q V5-V6 greater than or equal to 0.03 sec and Q/R ratio greater than 20 percent
- Inferior myocardial infarction (as per above criteria) and R-AVR greater than 0.1 mV

Subendocardial

- None present
- An ST segment depression greater than 0.1 mV horizontal or downward sloping, with duration greater than 0.08 sec. These ECG findings had to be present in 2 or more consecutive electrocardiograms, recorded at least 24 hours apart. Additional electrocardiograms preceding ECGs exhibiting normal ST segments or demonstrating regression of findings with normalization of ST segment during the hospitalization related to the qualifying event were necessary for the diagnosis. Evolution with normalization of ST and appearance or persistence of ischemic T wave in same anatomical area was codeable in this category.
- Presence of new ischemic T wave in anatomical area, persisting for more than 24 hours

Injury

Definition: An ST segment vector greater than or equal to 0.1 mV directed toward anatomical area and having an upward, convex morphology.

Code N if no criteria present.

Code 1 if criteria present.

All locations must be coded.

Anterior: Leads V1-V5

Lateral: Any of leads I, AVL, V5, V6

Anterolateral: Leads V1-V6 or V1-V4 and I, AVL, V5, V6

Inferior: Leads III, AVF (may also include lead II)

Posterior: (reciprocal changes in V1-V3 manifested by downward ST depression greater than 0.1 mV and 0.08 sec duration

Inferoposterior: Leads III, AVF, V1-V3 as expressed above.

Inferolateral: Leads III, AVF, V5, V6

Subendocardial: ST segment depression greater than 0.1 mV and 0.08 sec duration in any lead (except AVR)

Ischemia

Definition: An inverted and symmetrical T wave greater than or equal to 0.2 mV or a diphasic T wave with positive/negative morphology with a negative component greater than or equal to 0.2 mV.

Code N if no criteria present.

Code 1 if criteria present.

All locations must be coded.

Anterior: Leads V1-V4

Lateral: Any of leads AVL, I, or V5, V6

Anterolateral: Leads V1-V6 or V1-V4, any of I, AVL, V5, V6

Inferior: Leads III, AVF (may include lead II)

Inferoposterior: Leads III, AVF, V1-V3 (upright symmetrical T wave reflecting posterior wall reciprocal changes)

Inferolateral: Leads III, AVF, V5, V6

APPENDIX D

LABORATORY PROCEDURES

Bilirubin, Serum:

Total bilirubin was determined by the Gambino modification[10] of the method of Jendrassik and Grof using the AutoAnalyzer. Unconjugated bilirubin was diazotized with sodium nitrite and sulfanilic acid. A green color was developed using a strongly alkaline tartrate buffer and read on a spectrophotometer at 600 nm.

Glutamic Oxaloacetic Transaminase, Serum (SGOT):

SGOT was determined by the classic method of Henry et. al[11] with a few modifications. Serum was incubated with a substrate of L-aspartic acid. The resulting oxaloacetic acid was reduced by coenzyme I (NADH) and malic dehydrogenase to L-malic acid. This reaction rate was measured spectrophotometrically at 340 nm as NADH was oxidized to NAD using the GEMSAEC -- a centrifugal analyzer.

Cholesterol, Serum:

The samples were extracted by the procedure of Kessler and Lederer.[12] The cholesterol determination was based on the Lieberman-Burchard reaction and was done on the AutoAnalyzer II system. Since the total color yield of cholesterol ester was somewhat higher than that of free cholesterol, the serum samples were referred to a standard which contained only free cholesterol. This serum calibration sample related the value obtained on the Auto-Analyzer II to that of the reference Abell-Kendall method.[13]

Triglycerides, Serum:

Samples were extracted by the procedure of Kessler and Lederer.[12]

Triglycerides were measured fluorometrically on the AutoAnalyzer II after hydrolysis to free glycerol and subsequent oxidation of the glycerol to formaldehyde; formaldehyde was coupled with acetylacetone to give the fluorescent product 3,5-diacetyl-4-dihydrolutidine.[13]

Uric Acid, Serum:

Uric acid was determined using the Gochman and Schmitz method.[14] Uric acid was oxidized by uricase and the product, hydrogen peroxide, was oxidatively coupled with 3-methyl-2-benzothiazolinone hydrazone hydrochloride in the presence of peroxidase to produce a blue indamine dye. The absorbance was measured using an AutoAnalyzer at 600 nm.

Alkaline Phosphatase, Serum:

Alkaline phosphatase was determined by the method of Bowers and McComb.[15] Alkaline phosphatase catalyzed the hydrolysis of paranitrophenyl phosphate to paranitrophenol and inorganic phosphorus. The absorbance of paranitrophenol was measured using the GEMSAEC — a centrifugal analyzer at 404 nm.

Urea Nitrogen, Serum

A modification of the diacetylmonoxime-thiosemicarbazide method[16] was used for the measurement of urea. It was based on the direct reaction of urea and diacetyl monoxime under strong acidic conditions in the presence of thiosemicarbazide. The pink color of the resulting triazine derivative was read at 480 nm using an AutoAnalyzer.

Glucose, Serum:

Glucose was removed from other hexoses by a protein-free filtrate (Somogyi-Nelson). Glucose was then phosphorylated by hexokinase and excess adenozine triphosphate to glucose-6-phosphate. This was oxidized in the

presence of nicotinamide adenine dinucleotide (NAD) by glucose-6-phosphate hydrogenase to 6-phosphoglucono-W-lactone and NADH.[17] The degree of reduction of NAD to NADH, measured on the Abbott ABA-100 at 340-380 nm, provided a quantitative analysis of the glucose.

Total Salicylates, Urine:

This method was adapted from the procedure of Trinder[18] in which there was formation of a colored complex between ferric ions and an intact salicyl group, which was a component of aspirin and aspirin metabolites. The reaction with ferric ions in a 0.12 N HCL solution produced a violet color which was read at 540 millimicions in an AutoAnalyzer II.

Potassium, Serum:

Potassium was determined using a flame photometry on an I.L. Model #343 flame photometer, standardized against lithium standards.

Platelet Aggregation:

Epinephrine-induced platelet aggregation test was performed on a modified Chrono-Log, Model 330 Platelet Aggregometer, on fresh platelet rich plasma in each Clinical Center. In order to maintain study blindness, each Clinical Center recorded instrument output on a 2-channel cassette tape recorder employing an FM voltage to frequency converter. The tape cassettes were sent to the Central Laboratory where platelet-aggregation curves were generated and amplitudes of first and second phases of aggregation were determined. The amount of aggregation was expressed as a percentage of the amplitude between the platelet poor plasma baseline and the platelet rich plasma baseline.

APPENDIX E

STUDY FORMS*

Patient Information Sheet
Qualifying Myocardial Infarction Form
Initial Visit Form
Baseline Form
Follow-up Examination Form
Missed Visit Form
Nonfatal Event Forms
- Myocardial Infarction - Angina Pectoris
- Stroke
- Intermittent Cerebral Ischemic Attack
- Peripheral Arterial Occlusion
- Intermittent Claudication
- Pulmonary Embolism
- Cardiovascular Surgery
- Gastrointestinal Hospitalization Form

Hospitalization Form
Death Forms
- Death Notification Form
- Cause of Death Form
- Mortality Coding Form

Drug Requisition Form
Form Requisition
Dietary Instruction Sheet
- Fasting State
- Fat-Free State

Statement of Scheduled Interim Urine Specimen

*Study Forms are available upon request from the AMIS Coordinating Center, 600 Wyndhurst Avenue, Baltimore, Maryland 21210.

APPENDIX F-1

INDICATORS OF SEVERITY OF CORONARY HEART DISEASE

Criteria Committee of New York Heart Association: Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis, 6th Ed., Boston, Little, Brown and Co., 1964.

Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome are present even at rest. If any physical activity is undertaken discomfort is increased.

APPENDIX F-2

SOCIODEMOGRAPHIC CHARACTERISTICS

Race

For the purposes of this study, race was defined as follows:

1. White: Includes persons of Mexican birth or ancestry who are not Indian or other non-white race. Puerto Ricans who are not black are defined as white.

2. Black: Includes persons of mixed white and black parentage or mixed Indian and black parentage, unless accepted in the Indian community.

3. Other: American Indians, Asiatic Indians, Japanese, Chinese, Filipinos, and Koreans. Also included are persons of mixed white and Indian parentage if regarded as members of the Indian community.

Lifestyle

The patient's typical life style was defined as:

1. Sedentary: The sedentary person spends most of his or her waking hours in activites such as working at a desk, reading, watching television, or other quiet pursuits.

2. Light Physical Activity: This person walks about one mile a day, leisurely rides a bicycle, fishes, bowls, golfs, or engages in light carpentry, light gardening, light industrial work, teaching, or light housework.

3. Moderate Physical Activity: This person frequently engages in activities such as jogging, swimming, tennis, ice skating, heavy garden work, snow shoveling, carrying mail, working in building trades, or heavy industrial work.

4. Heavy Physical Activity: This person does the equivalent of active training in sports such as soccer, handball, ice hockey, basketball or engages in very heavy activities such as ditch digging, carrying heavy weights, very heavy farm work, mining, or working as a lumberjack.

APPENDIX F-3

MEDICAL HISTORY CHARACTERISTICS

Cigarette Smoking

The patient was considered a cigarette smoker if he or she had smoked at least 100 cigarettes in his or her lifetime.

An ex-smoker was defined as a person who had smoked more than 100 cigarettes in his or her lifetime but was not currently smoking cigarettes.

The patient was considered a nonsmoker if he or she had smoked fewer than 100 cigarettes in his or her lifetime.

Alcohol Consumption

The conditions listed below were based on an average alcoholic content of beer as 6 percent, wine as 15 percent, and liquor as 46 percent.

1. Two 12 oz. cans of beer equal approximately 1.5 oz. of pure ethyl alcohol.

2. Two 5 oz. glasses of wine equal approximately 1.5 oz. of pure ethyl alcohol.

3. Two mixed drinks equal approximately 1.5 oz. pure ethyl alcohol.

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