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COOPERATIVE STUDIES

Persantine-Aspirin Reinfarction Study. Part II. Secondary Coronary Prevention With Persantine and Aspirin

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In the Persantine-Aspirin Reinfarction Study, Part II (PARIS II), 3,128 persons who had recovered from myocardial infarction, suffered from 4 weeks to 4 months previously, were randomized into two groups: dipyridamole (Persantine) plus aspirin (n = 1,563) and placebo (n = 1,565). The average length of follow-up was 23.4 months. Prespecified primary end points were coronary incidence (definite nonfatal myocardial infarction plus death due to recent or acute cardiac event), coronary mortality (death due to recent or acute cardiac event) and total mortality, each at 1 year of patient follow-up and at the end of the study.

Coronary incidence in the Persantine plus aspirin group was significantly lower than in the placebo group, both at 1 year (30% reduction) and at the end of the study (24% reduction). The statistically significant differences in coronary incidence, at 1 year and at the end of the study, in favor of the combination treatment remained after adjustment for multiple baseline variables and adjustment for multiple testing (three end points for two time periods). Although there were reductions for other end points, these differences were not statistically significant. Coronary mortality was 20% lower in the Persantine plus aspirin group compared with the placebo group at 1 year, and 6% lower overall. Total mortality in the treated group compared with the placebo group was 11% lower at 1 year and 3% lower overall. The reduced rates of coronary incidence largely reflected lower rates of definite nonfatal myocardial infarction in the Persantine plus aspirin group.

Several subgroups were defined a priori and at the end of the study. The beneficial effect of Persantine plus aspirin compared with placebo for coronary incidence tended to be greater for the following groups of patients: those who had a non-Q wave infarct; those who were not taking digitalis; those who were receiving beta-receptor blocking drugs at baseline; those who were in New York Heart Association functional class I; those who had had only one myocardial infarction; or those who were enrolled in the study early, that is within 85 days of the qualifying myocardial infarction.

(J Am Coll Cardiol 1986;7:251–69)

The Persantine-Aspirin Reinfarction Study, Part II (PARIS II) was a randomized, controlled, double-blind trial designed to test the efficacy of the combination of Persantine (dipyridamole) and aspirin in the long-term therapy of coronary heart disease in men and women recently recovered from myocardial infarction. It has long been established that blood platelets, or more specifically platelet aggregation, play a fundamental role in initiating thrombus formation in arteries (1,2). Acute myocardial infarction and sudden death may be a result of platelet aggregates forming in arteries or in the microcirculation of the heart. It is reasonable to expect that if the incidence of thrombosis and embolization is reduced, then, perhaps as a consequence, mortality and morbidity from myocardial infarction will be reduced. The latter possibility is the rationale for testing the hypothesis that long-term inhibition of platelet aggregation in high risk individuals may have a beneficial effect.

Dipyridamole and aspirin both influence platelet function in ways that impede thrombogenesis (3–12) and are promising antithrombotic agents for prophylactic use in preventing arterial thrombosis in humans. Additionally, dipyridamole and aspirin appear to potentiate each other's inhibitory effects on thrombosis in small vessels (13–15). A dose-dependent increase in the potentiation of dipyridamole by aspirin has been reported with dosages approximately the same as those used in this study (16). The combination has been shown to be successful in reducing the rate of occlusion of coronary artery bypass grafts (17,18).

The first Persantine-Aspirin Reinfarction Study (PARIS)

*A list of contributing investigators and participating centers of the Paris II Research Group appears in the Appendix

This study was supported by an unrestricted grant from Dr Karl Thomae, GmbH, Biberach/Riss, West Germany. This paper was presented at the American College of Cardiology Annual Meeting, March 13, 1985, Anaheim, California

Manuscript received April 2, 1985, revised manuscript received August 29, 1985, accepted September 10, 1985.

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0735-1097/86/$3 50

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(to avoid confusion, the original PARIS will heareafter be referred to as PARIS I), completed in 1979, evaluated a combination of Persantine (dipyridamole) and aspirin (19). Patients were randomized 8 weeks to 5 years after an acute myocardial infarction to treatment with Persantine plus aspirin, aspirin alone or placebo. At the end of PARIS I, rates of death, coronary death (death due to recent or acute cardiac event) and coronary incidence (defined as definite nonfatal myocardial infarction or coronary death) were lower for both active treatment groups compared with the placebo group, but the differences were not statistically significant at the end of the study. Differences in rates of coronary incidence between placebo and the Persantine-aspirin combination treatment for the first 24 months of treatment were statistically significant. The combination treatment showed a small nonsignificant advantage over aspirin alone for coronary mortality and coronary incidence for the first 20 months of treatment. Post hoc analyses showed that the subgroup of patients enrolled within 6 months of their qualifying myocardial infarction who were randomized to active treatment, particularly the Persantine-aspirin group, had the largest absolute and proportionate reductions in total and coronary mortality.

At the conclusion of PARIS I, the study Policy Board recommended to the sponsor that another study of Persantine and aspirin be conducted with patients enrolled closer in time to their qualifying myocardial infarction. The design of the study was finalized based on detailed review of the issues of number of patients required, recruitment potential, statistical power, cost and the state of knowledge concerning the efficacy of antiplatelet drugs after completion of the Aspirin Myocardial Infarction Study (AMIS) (20) and PARIS I (19). These considerations led to a two-group design, rather than the three-group design of PARIS I, with 3,000 patients to be randomized to dipyridamole plus aspirin or to placebo. The primary aim was to test the efficacy of dipyridamole plus aspirin compared with placebo in persons aged 30 to 74 years recruited within 4 weeks to 4 months of a verified myocardial infarction. Three end points, each to be examined after 1 year of patient follow-up and for the total follow-up period, were selected as the determinants of efficacy. These end points were total mortality, coronary mortality, and coronary incidence as defined for PARIS I. Thus, there were six primary end points, three defined events for each of two specified time periods.

In addition, three a priori subgroup hypotheses were formulated based on findings of PARIS I which indicated a greater benefit in patients at lower risk of subsequent reinfarction, namely: 1) active medication would be more beneficial in patients who had had only one myocardial infarction (the one that made the patient eligible for PARIS II) compared with those with a history of one or more myocardial infarctions before the one that made the patient eligible for PARIS II; 2) efficacy would be greater in patients classified in New York Heart Association functional class I (no limitation of ordinary physical activity) versus class II (slight limitation) (21); and 3) efficacy would be greater in patients not taking digitalis at entry compared with those taking this drug. During the course of recruitment for the trial it became evident that a sizable proportion of eligible patients were receiving treatment with a beta-receptor blocking agent, and a further hypothesis was formulated based on interim findings (October 1982 data), namely: 4) dipyridamole and aspirin would be more efficacious in patients prescribed beta-receptor blocking agents compared with those not using such medication at baseline.

Methods

Study organization. Nineteen of the original 20 PARIS I clinics agreed to participate in PARIS II. The Policy Board selected an additional 12 clinics to bring the total number to 31 (25 in the United States and 6 in Great Britain). The PARIS I Coordinating Center at the Maryland Medical Research Institute in Baltimore, Maryland, the Central Laboratory at Bio-Science Laboratories in Van Nuys, California, the ECG Reading Center at the Laboratory of Physiological Hygiene at the University of Minnesota and the Data Audit Center (formerly the Data Quality Control Center) at the University of Chicago also participated in the second study (22). Participating institutions and staff and committee members are listed in the appendix.

Patient eligibility criteria. Men and women were eligible for enrollment if they satisfied the following conditions:

1) Age 30 to 74 years at the initial visit.

2) A clinical history, including serum enzyme elevations, compatible with a diagnosis of myocardial infarction and significant electrocardiographic changes determined locally and verified by the study ECG Center (22).

3) Time since last documented myocardial infarction of 4 weeks to 4 months.

4) Cardiac disease evaluated at the initial visit was class I or class II in the 1964 functional classification system of the New York Heart Association. Class I includes 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 includes patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain (21).

5) No previous cardiac or coronary surgery, prosthetic valve insertion or permanent pacemaker implantation. (No other cardiovascular surgery made an individual ineligible.)

6) Freedom from life-limiting diseases, that is malignancy, severe pulmonary insufficiency or chronic hepatic

disease. Patients with maturity-onset diabetes were eligible even if they were insulin dependent.

7) Free from conditions that would affect long-term follow-up, such as cerebral vascular disease, psychosis, alcoholism or orthopedic disability.

8) Free from conditions requiring continuing regular use of platelet-affecting drugs.

9) Free from aspirin hypersensitivity.

10) Free from upper gastrointestinal bleeding or history of clinically significant episodes of bleeding.

11) Willing to forego use of aspirin or other platelet-affecting drugs during the study. The patient's physician must also have agreed that it was feasible for the patient to avoid nonstudy aspirin-containing compounds and other platelet-affecting drugs. Acetaminophen was provided by the study for patients to use in lieu of aspirin for pain relief.

12) Not on anticoagulant therapy.

13) Free from postural hypotension.

14) Systolic blood pressure less than 200 mm Hg and diastolic blood pressure less than 115 mm Hg at the baseline visit.

15) Women not of childbearing potential.

16) Willing to make scheduled follow-up visits for at least 1 year after orientation session.

17) Willing to give written informed consent.

Patients were accepted regardless of the number of previous myocardial infarctions or presence of complications during the acute event, provided all other eligibility criteria were satisfied. If the patient had been recently hospitalized for symptoms suggestive of a myocardial infarction, he or she must have been discharged before the initial visit was completed. In most clinics, the candidates screened for eligibility were patients of the study investigators. The sources for recruitment varied by clinic, but were the same as those utilized for PARIS I (22).

Treatment allocation and dosage regimens. Each patient, after the Coordinating Center staff verified his or her eligibility, was randomly allocated to one of two treatment groups: Persantine plus aspirin or placebo. The number of patients allocated to these two groups was 1,563 and 1,565, respectively. The patients in the combination treatment group were asked to take one Asasantine capsule three times a day. Each Asasantine capsule contained 75 mg of dipyridamole and 330 mg of aspirin. Each patient in the placebo group also was asked to take one capsule three times a day. The placebo capsules were identical in appearance to Asasantine capsules, but contained lactose. The study was double-blind with neither the Clinical Center staff nor the patient knowing the content of the assigned capsules.

The randomization schedules used to assign eligible patients to treatment were prepared by the Coordinating Center staff before the trial started and were different for each clinic. The schedules provided for balance in the number of patients to be assigned to each of the two treatment groups in each clinic using blocks of size eight. No other stratification variables were used.

Examination schedule. Two initial visits were scheduled to collect extensive baseline data including a 12 lead rest electrocardiogram (22). Randomization occurred at the second of these visits, when the patient's eligibility was confirmed and the treatment allocation was obtained (by opening the treatment allocation envelope sent from the Coordinating Center or by calling the Coordinating Center).

Follow-up appointments were scheduled at 1 month and then at 4 month intervals after entry. Each visit included medical history, physical examination, assessment of adherence to study prescription, local laboratory determinations (hematocrit, white blood cell count, hematuria, urine glucose, urine protein) and collection of urine specimens for determination of salicylate and dipyridamole levels at the Central Laboratory. In addition, at annual visits, fasting blood samples were taken and serum specimens forwarded to the Central Laboratory for biochemical analyses (urea nitrogen, uric acid, creatinine, cholesterol, glucose, potassium, serum glutamic oxaloaceticacid transaminase (SGOT) and total bilirubin). A 12 lead rest electrocardiogram was taken at the patient's last follow-up visit. Data were recorded on standardized forms and sent to the Coordinating Center. Copies of key forms also were sent from the Clinical Centers directly to the Data Audit Center (22).

Adherence to study prescription was assessed at each follow-up visit by a pill count, questioning of the patient by the physician, and collection of urine specimens to be analyzed at the Central Laboratory for dipyridamole and salicylate metabolites. The results of these latter tests were forwarded only to the Coordinating Center and not to the clinic. These tests were also conducted on baseline specimens to verify that patients were not using aspirin or dipyridamole at the time of enrollment.

The urine salicylate test is useful to detect the recent ingestion of aspirin, but this test will probably not detect aspirin taken more than 8 to 12 hours before the time of the urine specimen. Positive tests also occur with other salicylate-containing drugs. In this study, aspirin and dipyridamole were given in a single capsule so a positive test for dipyridamole would be sufficient evidence that a patient was taking the assigned active medication. A positive salicylate test could indicate adherence to the active medication but might also indicate that the patient was taking known aspirin.

The primary end points were total mortality, coronary mortality and coronary incidence at 1 year of patient follow-up and for the total study follow-up period. Coronary mortality was defined as death due to an acute or recent cardiac event, that is, a cardiac event that resulted in death within 24 hours of the onset of symptoms or later if the death occurred during an uninterrupted hospital stay for a cardiac event. Coronary incidence was defined as definite nonfatal myocardial infarction or coronary death. Other nonfatal car-

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diovascular events such as suspect recurrent myocardial infarction, acute coronary insufficiency, angina pectoris, congestive heart failure, stroke, pulmonary embolism and cardiovascular surgery were also monitored. Definitions of fatal and nonfatal events were given in a previous report (22). Reports of mortality, myocardial infarction, acute coronary insufficiency, angina pectoris with hospitalization and stroke were reviewed by the study Mortality and Morbidity Committee without knowledge of treatment assignment. This committee classified each event according to previously defined criteria (22). In cases of disagreement between the study physician and this committee, the committee's classification was taken as final. At least semiannually, data reports were prepared at the Coordinating Center and independently at the Data Audit Center for review by the Data Monitoring Committee. The reports included data on the incidence of end points, possible side effects and drug reactions, biochemical analyses, quality control and patient adherence to protocol prescription. Any disagreements between the Coordinating Center and Data Audit Center reports were also reviewed at these meetings.

Study timetable. The original study plan was to enroll patients over a 1 year period beginning in October 1980 and to follow all patients to a common termination date in October 1983. Recruitment was slower than expected, perhaps partly because of the increase during the 1980s in early treatment after myocardial infarction with coronary artery bypass graft surgery and because patients with a history of bypass surgery were not eligible for the study. To enroll 3,000 patients, the recruitment period was extended to July 1983. The follow-up phase of the study was extended to July 1984 so that every patient would have at least 1 full year of follow-up. At the time of the decision to extend the recruitment and follow-up periods (December 1982), the Policy Board also decided to terminate each patient's follow-up at a closeout visit coinciding with the scheduled second annual follow-up visit. Those relatively few patients who had already completed 2 years of follow-up had a closeout visit at their next scheduled follow-up visit. Beginning in March 1984 and continuing through July 1984, all patients, including those who had not completed 2 years of follow-up, were scheduled for a closeout visit with the proviso that no patient would have a closeout visit until he or she had completed a full year of follow-up. Study treatment was discontinued at the closeout visit but neither the patients nor the Clinical Center staff were unblinded as to individual treatment assignments until August 1984. Deaths and other end points were not counted if the event occurred after a patient's closeout visit or, in the absence of a closeout visit, if the event occurred after July 31, 1984, the final cutoff date for the study. Analyses presented here are based on the data file as of October 31, 1984. All patients were always counted in the treatment groups to which they were originally randomized, regardless of considerations such as adherence to study medications or completeness of follow-up.

Protocol violations. There were five known protocol violations in connection with treatment allocation. In one case, an allocation was given by telephone to a third party in the Clinical Center, but the patient had not in fact completed the baseline examination. The patient was not entered into the study and was immediately lost to follow-up. In four other cases, a Change of Status form was submitted to the Coordinating Center from a Clinical Center prior to completion of the baseline examination, indicating that the patient was no longer eligible for the study. However, the treatment allocation envelopes were returned opened to the Coordinating Center. These patients were also not entered into the study. In all five cases, only coded bottle numbers, and not actual treatment assignments, were disclosed. The life-death status of the latter four persons has been obtained and all were alive as of July 31, 1984.

Data Audit Center review of nonfatal myocardial infarction. At the close of the study, the Data Audit Center conducted a special review of the classification of nonfatal events by the Mortality and Morbidity Committee. This review had two objectives: 1) clarification of the specific criteria used by the committee to diagnose definite myocardial infarction, and 2) verification that all events classified by the committee as definite myocardial infarction met these criteria and that all events not classified as definite myocardial infarction did not meet these criteria. The findings of this review are presented at the end of the Results section.

Power and other statistical considerations. Power calculations were made at the beginning of the study assuming a 25% reduction in rates for the Persantine and aspirin group compared with the placebo group for the primary end points. Approximate 2 year PARIS I placebo rates were projected for the PARIS II placebo group; these were 8.0, 7.0 and 14.0% for death, coronary death and coronary incidence, respectively. Equal sample sizes of 1,500 were assumed for a two-sided Z test of two proportions at the 0.05 level, that is, using a critical value of 1.96. Power of this test for total mortality, coronary mortality and coronary incidence was calculated as 0.54, 0.48 and 0.81, respectively. However, it was clear that a critical Z value of 1.96 would be inappropriate because six primary end points were specified and there would be periodic data monitoring and statistical testing during the course of the study. To take account of this analysis plan, a computer simulation procedure was developed to select an appropriate Z value to apply to the six primary analyses at the end of the study. A critical Z value of 2.49 was derived (23). Power has not been determined exactly for this model but might be expected to be not much reduced from that using a single Z test with a critical value of 1.96 because even though the critical value used here

was much larger, there were more tests and hence more opportunities to surpass the critical value.

Life table rates were calculated using the product-limit method (24). Since all patients completed at least 1 full year of follow-up, the 1 year life table rates are the same as the crude rates derived by dividing the number of events in the first year of follow-up by the total number of patients in the group.

The following formulas were used to compute 95% confidence limits (L_1, L_2) on the percent difference between proportions (p_1, p_2) of events in the two treatment groups, with n_1 and n_2 patients in the two groups:

$$L_1 = 100\,[(e^{M_1}) - 1] \text{ and } L_2 = 100\,[(e^{M_2}) - 1],$$

where

$$M_1 = \ln(p_1/p_2) - 1.96\,S,\ M_2 = \ln(p_1/p_2) + 1.96\,S,$$

and

$$S = \left[\frac{1-p_1}{p_1 n_1} + \frac{1-p_2}{p_2 n_2}\right]^{1/2}.$$

These formulas give results similar to those derived using Fieller's theorem (25), but are easier to calculate.

For the primary end points, life table curves for the two treatment groups were compared using the Cox regression method (26) to compute the regression coefficient for treatment effect. This method was also used to adjust treatment effects for differences in the distributions of various baseline variables between the two treatment groups. Baseline variables were selected for inclusion in the Cox model as adjusting variables (covariates) following the principles discussed by Canner (27). Adjustment for a covariate can be expected to alter the estimated treatment effect only if that covariate is *influential* (a change in that covariate corresponds to a change in probability of that event) and also *disparate* (the covariate is not distributed the same in both treatment groups). Canner (27) showed that, under reasonable assumptions, the magnitude of the effect of adjustment for a given covariate is proportional to the product of the Z value for influence and the Z value for disparity. In the present study, every covariate showing significant disparity (absolute Z value >1.96) was included in the set used for adjustment. In addition, for each primary end point, influential covariates were selected using a step-up regression procedure (28). The variables considered in the regression procedure were those 25 which yielded the highest products of the two Z values. From this latter set, the ones selected were those which showed significant influence on the end point in the regression analysis.

The treatments were also compared in subgroups of patients defined by baseline characteristics. Specifically, certain baseline variables were used to divide patients into two subgroups, for example, digitalis users and nonusers. Then the Persantine plus aspirin versus placebo difference in incidence of the end point in the first subgroup was compared with that difference in the second (complementary) subgroup. A Cox regression model (26) was used to evaluate whether treatment effects were different in the two subgroups or whether the treatment could be considered as having a common effect in both subgroups.

Three prior subgroup hypotheses were specified at the beginning of the trial. Based on six primary tests of significance (three end points examined at two time points) and three subgroup hypotheses, the critical Z value was determined to be 2.86 for each test of these subgroup comparisons. Tests of significance for the three end points examined at two time points for all other subgroup hypotheses not specified a priori were determined to have a critical Z value of 3.53. These critical values (2.86 and 3.53) are appropriate for tests to determine whether the Persantine-aspirin treatment effect in one subgroup is different from the treatment effect in the complementary subgroup (such as given in column 4 of Table 9); they are not appropriate for testing the treatment effect *within* a given subgroup (such as given in column 3 of Table 9).

Results

Baseline comparability of treatment groups. Of 179 baseline characteristics examined, only 13 (7.3%) showed a difference in distribution between the two treatment groups with a probability value of less than 0.05, which is consistent with statistical expectation (Table 1, Part I). Thus, there is no reason to question the efficacy of the randomization. The mean time from qualifying myocardial infarction to entry into the study was 83 days (83.5 for the combination treatment group and 82.4 for the placebo group). The 13 variables which showed some imbalance between treatment groups were listed in Part I of Table 1 and were used as covariates in the regression analysis for all end points.

Additional variables were selected for each end point as outlined in Methods. Table 1, Part II compares the distribution between the two treatment groups of other variables selected as covariates for one or more of the Cox regression analyses. Variables used for adjustment in the analyses of total mortality are indicated by letter A in the right-hand column of Table 1; the variables used for adjustment of analyses of coronary mortality and coronary incidence, by letters B and C, respectively.

For comparison of the two studies, variables selected for adjustment in PARIS I (19) that were not included as covariates for PARIS II analyses are given in Table 1, Part III. The distribution of other baseline characteristics that may be considered to be clinically important are given in Table 1, Part IV.

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Table 1. List of Baseline Characteristics Selected as Adjusting Variables

Baseline Variable	PR/A	PLBO	Z Value PR/A-PLBO	End Point Adjusted*
I. Variables with Z value ≥ 1.96				
1 Categorical variables (% of patients)				
Marital status, married	76.8	80 0	−2.19	A,B,C
Pleural effusion	2 4	1.2	2.43	A,B,C
Use of oral hypoglycemic agents	5 0	3.1	2.74	A,B,C
Use of digitalis	15.6	13.1	2.00	A,B,C
X-ray abnormalities (other than pleural effusion, pulmonary congestion or cardiomegaly)	12.7	9.8	2.56	A,B,C
Normal chest X-ray	73.4	77.0	−2.34	A,B,C
Cardiac arrest during previous MI	3.8	5.6	−2.44	A,B,C
Symptoms of MI after qualifying exam	2.0	0.6	3.42	A,B,C
Use of acetaminophen after qualifying exam	23 7	20 7	2.04	A,B,C
ECG evidence of new MI after qualifying exam	1 6	0.5	2.98	A,B,C
2. Continuous variables (mean value)				
Serum urea nitrogen/creatinine ratio	15.1	14.8	2.56	A,B,C
Inorganic phosphorus (mg/dl)	3.4	3.3	2.06	A,B,C
Hematocrit (%)	44.3	44.7	−2.25	A,B,C
II. Other variables selected as adjusting variables				
1. Categorical variables (% of patients)				
Three or more previous MIs	3.3	2.6	1.06	B,C
ST depression (Minnesota Code 4.1 to 4.4)	22.0	20.7	0.92	A,B
Employment status: full time	32.6	33.4	−0.47	A,B
Persistent supraventricular rhythm (Minnesota Code 8.4.1)	0.1	0.1	0.00	C
Peripheral edema	1.1	1.5	−1.10	C
History of angina pectoris	45.8	43.6	1.26	A
History of sinus node dysfunction	1.5	1 2	0.77	B
History of stroke	1.7	1 5	0.57	C
History of frequent VPBs (6 or more/min)	11.4	12 4	−0.87	C
2. Continuous variables (mean value)				
Heart rate on ECG (beats/min)	66.3	65.8	1.00	A,B,C
Maximal S depth (mm) in leads V_1, V_2, V_3	2.4	2.3	0.03	A,B,C
Ectopic codes, T-R′ interval (mm)	6.2	6.4	−0.96	A,B,C
Age (yr)	56.8	56.5	0.89	A,B
Serum urea nitrogen (mg/dl)	17.2	16.9	1.86	C
Serum uric acid (mg/dl)	6.9	6.9	−0 99	A
III. Other variables selected for adjustment in PARIS I				
1. Categorical variables (% of patients)				
Physical activity: light or sedentary	70.5	71.9	−0.89	—
Use of antiarrhythmic agents	13.6	13.0	0.44	—
Use of insulin	3.7	3.8	−0.09	—
Major Q/QS patterns (Minnesota Code 1.1.1 to 1.1.7)	21.6	20.9	0.48	—
ST elevation (Minnesota Code 9.2)	3.1	2.8	0.53	—
High amplitude R waves (Minnesota Code 8.1 1 to 8.1 5)	4.1	4.4	−0 44	—
Use of beta-receptor blocking drugs	44.6	44.2	0.25	—
Cardiomegaly on baseline chest X-ray	14.8	12.4	1.94	—
Ectopic codes (runs or bigeminy)	15.1	13.6	1.13	—
2. Continuous values (mean value)				
Body mass index	26.4	26.4	−0.29	—
Male	26.4	26.4	−0 43	—
Female	26.6	26.5	0.11	—
Pulse rate (counts/min)	70.4	69 9	0.20	—
Serum glucose (mg/dl)	108.4	106.1	1.81	—
Absolute neutrophil count	(not measured in PARIS II)			

(continued)

Table 1 (*continued*)

Baseline Variable	PR/A	PLBO	Z Value PR/A-PLBO	End Point Adjusted*
IV Other variables which may be clinically important				
1. Categorical variables (% of patients)				
Male	83.0	84.7	−1 28	—
White	90.0	89.5	0.52	—
Age ≥ 60 yr	41.1	39.4	0.94	—
No history of MI prior to qualifying MI	84.4	84.9	−0.36	—
New York Heart Association class I	51 9	52.8	−0.50	—
History of ECG-documented arrhythmia	35.1	35.3	−0.09	—
History of congestive heart failure	10 4	9.5	0.85	—
History of coronary arteriography	16.5	17.3	−0.56	—
History of intermittent claudication	4.9	5.1	−0.24	—
Use of long-acting antianginal medication	37.7	35.4	1.33	—
Use of nitroglycerin or other coronary vasodilators	44.7	45 4	−0.36	—
Use of diuretic drugs	28.2	28.6	−0.29	—
Use of antihypertensive medication other than diuretics	4.9	5.1	−0.24	—
Use of aspirin less than once a month	79.5	79.4	0.03	—
2. Continuous variables (mean value)				
Serum creatinine (mg/100 ml)	1.2	1.2	0.33	—
Serum cholesterol (mg/100 ml)	245.0	244.0	0.57	—
Serum potassium (mEq/liter)	4.6	4.5	0.62	—
SGOT (units)	33.2	33.7	−0.83	—
Serum total bilirubin (mg/100 ml)	0 7	0 7	−1.42	—
V Qualifying ECG classification (% of patients)				
Q/QS findings	71 3	69.7	0.96	—

*Used for adjustment of (A) total mortality analysis, (B) coronary mortality analysis, (C) coronary incidence analysis. ECG = electrocardiogram; exam = examination; MI = myocardial infarction; PLBO = placebo group, PR/A = Persantine-aspirin group, SGOT = serum glutamic oxaloaceticacid transaminase; VPBs = ventricular premature beats

Follow-up and adherence. Of the 3,128 patients enrolled, 2,726 completed the closeout visit and 225 were reported as deceased, leaving 177 to be accounted for. Of these 177 patients, 151 were reported by the Clinical Centers to be alive as of July 31, 1984, 141 having been contacted directly. Of the 26 remaining patients, another 18 were subsequently traced by a search agency and found to be alive. Thus, the vital status of only eight patients (six in the Persantine plus aspirin group and two in the placebo group) was not known at the time the files were closed for the data analysis for this report (October 31, 1984). Four of these patients (three in the Persantine plus aspirin group and one in the placebo group) completed 1 year of follow-up. All eight patients were counted as alive for this report.

Overall, only 8.5% of scheduled study visits were not completed. The mean time on study, measured for each patient from baseline examination to closeout visit (or July 31, 1984, if the closeout visit was not completed), was 23.4 months.

Adherence to study prescription was assessed at each follow-up visit by pill count, questioning of the patient by the physician and testing for urine levels of drugs. The clinic physician assessments indicated that patients in the Persantine plus aspirin and placebo groups, respectively, took 69.8 and 74.3% of all capsules called for by the protocol. The percent of patients taking less than 20% of all capsules during the first year was 12.5 in the combination treatment

Table 2. Distribution of Cumulative Percent of All Possible Capsules Taken at 1 Year and at 2 Years

Cumulative Percent	Percent Patients PR/A	PLBO
At 1 Year		
≥80	64.2	71.8
60 to 79	10 3	9.8
40 to 59	6 3	4.7
20 to 39	6.7	4.4
<20	12.5	9.2
At 2 Years		
≥80	59.8	67.5
60 to 79	11.3	10.0
40 to 59	6 0	5.8
20 to 39	8 0	5.2
<20	14 9	11 4

PLBO = placebo group; PR/A = Persantine-aspirin group

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Table 3. Biochemical Assessment of Adherence (number of patients tested in parentheses)

	Percent Patients	
	PR/A	PLBO
Urinary salicylate >10 mg/dl		
Baseline visit	14.7 (1,521)	14.1 (1,507)
First follow-up visit (4 mo)	77 9 (1,420)	10 7 (1,445)
First annual visit	69 9 (1,314)	13.1 (1,299)
Second annual visit	68.0 (855)	13 0 (849)
Urinary dipyridamole positive		
Baseline visit	2 7 (1,514)	2.3 (1,501)
First follow-up visit (4 mo)	71 0 (1,415)	2.2 (1,439)
First annual visit	67.3 (1,302)	4 4 (1,283)
Second annual visit	61 5 (847)	3.2 (840)

PLBO = placebo group; PR/A = Persantine-aspirin group.

group and 9.2 in the placebo group; the corresponding percent for 2 years was 14.9 and 11.4, respectively (Table 2).

At baseline, 2.5% of patients had a positive urinary dipyridamole test (Table 3); in PARIS I 1% of patients had a positive test at baseline. These data suggest that the false positive rate is approximately 2 to 3%, although it is possible that a few patients were taking dipyridamole at the time of the baseline examination. The follow-up false positive test results for patients in the placebo group ranged from 2.2 to 4.4% (Table 3). These results are consistent with the baseline findings and indicate that patients receiving placebo were not taking dipyridamole. The urinary dipyridamole results for the patients in the combination treatment group are consistent with the estimates of adherence based on pill count and questioning of the patient.

The results for urinary salicylate at baseline indicated a higher percent of patients with levels greater than 10 mg/dl (14%) compared with the 5% observed at baseline in PARIS I. The PARIS II data may indicate that a small proportion of patients were taking aspirin or other salicylate-containing drugs at baseline. In the placebo group, the proportion of patients with positive urinary salicylate levels at the follow-up visits was about the same as at baseline. In the Persantine plus aspirin group, the proportion of patients with a positive urinary salicylate level was similar to the proportion with a positive dipyridamole level.

During the first 2 years of follow-up, the proportion of patients reported using nonstudy aspirin-containing compounds or platelet-affecting drugs (dipyridamole, sulfinpyrazone, phenylbutazone, indomethacin) during any given follow-up period was 7% or less. The differences between treatment groups were minor.

Primary end points. Table 4 gives the percent for each treatment group (and Z values for the differences between percentages) of the fatal and nonfatal end points as classified by the Mortality and Morbidity Committee. With an average

Table 4. Death by Cause and Nonfatal Events as Classified by the Mortality and Morbidity Committee

	Percent Patients		Z Value	Percent Difference
	PR/A (n = 1,563)	PLBO (n = 1,565)	PR/A vs. PLBO	PR/A vs. PLBO
Death				
All causes*	7.1	7 3	−0.20	−3
All cardiovascular	6.1	6 6	−0.58	−8
All noncardiovascular	0.9	0.6	0 82	50
Cause unknown	0 1	0.1	0 001	0
Coronary heart disease*	4.9	5.2	−0.40	−6
Sudden coronary	2.4	2.0	0.61	20
Nonsudden coronary	2.6	3.2	−1.06	−19
All cancer	0.8	0.5	0.90	60
Other noncardiovascular	0.1	0.1	0.001	0
Definite nonfatal MI	4 5	7 1	−3.05	−37
Definite or suspect MI	4 8	7.5	−3.19	−36
Definite ACI	1.8	1.3	1.01	38
Definite or suspect ACI	6.0	5.6	0.54	7
Definite AP with hospitalization	2.9	3.5	−0.81	−17
Definite or suspect AP with hospitalization	3.6	4 1	−0.74	−12
Definite stroke	1.3	2.1	−1.64	−38
Definite or suspect stroke	1.3	2 3	−2.00	−43
Coronary incidence*	9.0	11.8	−2.57	−24

*Primary end point. Coronary incidence defined as definite nonfatal myocardial infarction (MI) or death due to recent or acute cardiac event. ACI = acute coronary insufficiency; AP = angina pectoris; PLBO = placebo group; PR/A = Persantine-aspirin group; vs. = versus.

follow-up of 23.4 months, the percent of patients who died was 7.1 for the Persantine plus aspirin group (111 deaths) and 7.3 for the placebo group (114 deaths) (Table 4).

Life table rates for death, coronary death, and coronary incidence are given in Figure 1 and Table 5; percent differences in rates and their confidence limits at each time point are also given. The first year rates for death were 4.2% for the Persantine plus aspirin group and 4.7% for the placebo group with a Z value for the difference of −0.60. The 2 year life table rates for death were 7.5% for the combination treatment group and 7.3% for the placebo treatment group with a Z value for the difference of 0.20. The Cox Z values comparing the life table curves were −0.20, unadjusted, and −0.47, adjusted for 22 baseline variables.

For coronary death (about 70% of the total deaths), there was a 6% reduction at the end of the study in the combination treatment group compared with the placebo group (Z = −0.40, Table 4) and a 20% reduction in the 1 year life table rates (Z = −1.11, Table 5). The corresponding 2 year rates were 5.2 and 5.5%, respectively (Z = −0.28). The Cox Z values comparing the two curves were −0.40, unadjusted, and −0.77, adjusted for 21 variables.

Coronary incidence for the Persantine plus aspirin group compared with the placebo group was reduced by 24% at the end of study (Z = −2.57, Table 4), by 30% for the 1 year life table rates (Z = −2.65, Table 5) and by 25% for the 2 year life table rates (Z = −2.67, Table 5). The Cox unadjusted Z value was −2.57 and the Z value adjusted for 22 baseline variables was −2.61. The treatment differences at 1 year and at end of study for coronary incidence were statistically significant by study criteria.

The 2 year life table rates are quite comparable with the percent of patients with events at the end of study, as would be expected, since most patients were followed for close to 2 years and only a few patients had a follow-up visit after the second annual visit. In all cases, the life table rates are slightly higher, but the treatment differences are of the same order of magnitude and the Z values are comparable.

Other fatal and nonfatal events. Drug-placebo differences for cause-specific mortality were small. For nonfatal

Table 5. End Point Life Table Rates, Z Values and Percent Reduction

	Event Rates		Z values	Percent Difference*	95% Confidence Limits for Percent Difference	
	PR/A	PLBO	PR/A vs PLBO	PR/A vs. PLBO	Lower	Upper
Total death (mo)						
4	1 6	1 7	−0 28	− 6	−46	59
8	2.8	3 3	−0 81	−15	−43	27
12	4.2	4 7	−0 60	−11	−35	26
16	5.1	5 3	−0 29	− 4	−30	30
20	5 9	6 3	−0 46	− 6	−31	28
24	7.5	7 3	0.20	3	−24	38
Coronary death (mo)						
4	1.3	1 3	0 17	0	−43	94
8	1 9	2 6	−1 22	−27	−53	20
12	2 8	3 5	−1 11	−20	−46	19
16	3.6	4 0	−0.69	−10	−39	27
20	4.1	4 6	−0 65	−11	−38	30
24	5.2	5 5	−0 28	− 5	−33	36
Coronary incidence† (mo)						
4	2 1	3 0	−1.61	−30	−55	9
8	3 5	5 6	−2 83	−38	−55	−13
12	5.5	7 9	−2 65	−30	−47	− 8
16	7.2	9.1	−1.94	−21	−38	1
20	8 4	10 7	−2 14	−21	−39	− 1
24	9 5	12 7	−2 67	−25	−42	− 4
Definite nonfatal myocardial infarction (mo)						
4	0 8	1 8	−2.41	−56	−77	−13
8	1 7	3 4	−3 03	−50	−70	−21
12	3.0	5 0	−2 81	−40	−59	−14
16	3.9	5 8	−2 30	−33	−51	− 5
20	4.8	7.0	−2 49	−31	−52	− 5
24	5 2	8 2	−3 03	−37	−55	−11

*$\frac{\text{PR/A rate} - \text{PLBO rate}}{\text{PLBO rate}} \times 100$. †Coronary incidence defined as definite nonfatal myocardial infarction and death due to recent or acute cardiac event. PLBO = placebo group, PR/A = Persantine-aspirin group, vs. = versus

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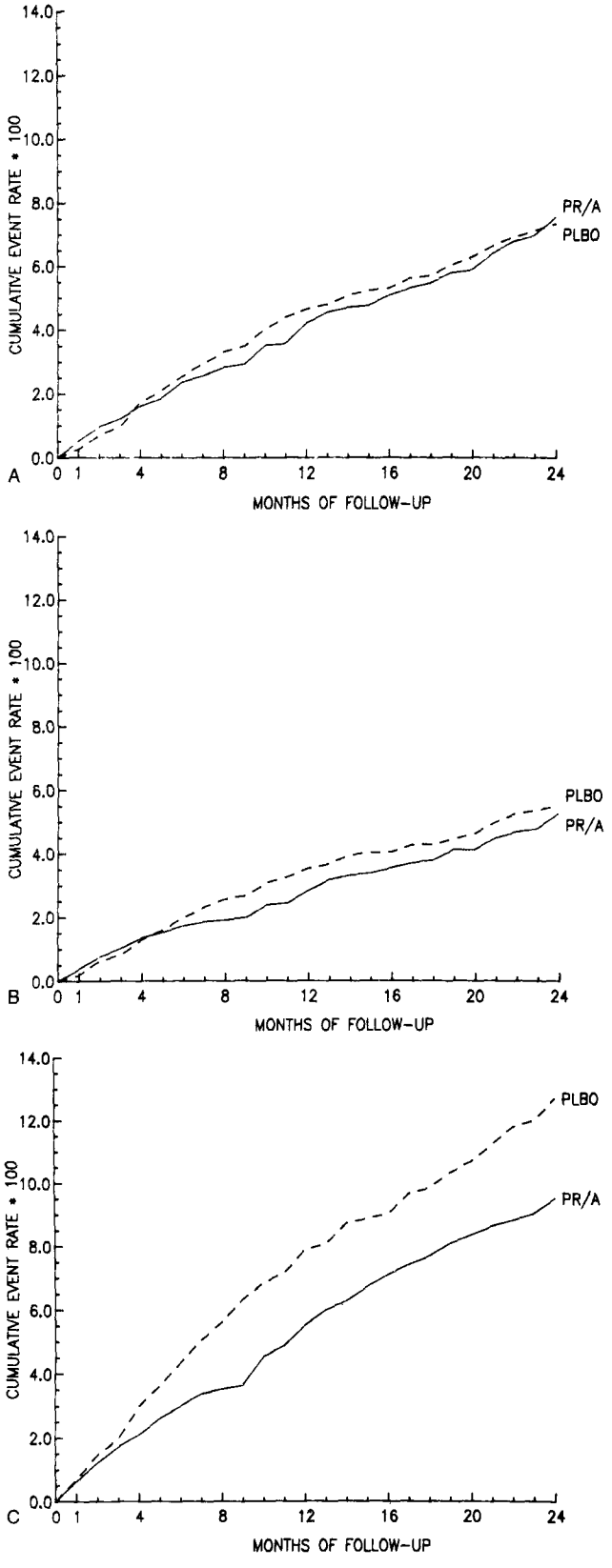

Figure 1. Cumulative event rates, all patients. **A**, Death, all causes; **B**, coronary death; **C**, coronary incidence. PLBO = placebo; PR/A = Persantine-aspirin group.

events classified by the Mortality and Morbidity Committee, the differences for definite nonfatal myocardial infarction and for the combination of definite and suspect nonfatal myocardial infarction yielded Z values of −3.05 and −3.19, respectively (Table 4). The first year rates were 3.0 for Persantine plus aspirin and 5.0 for placebo patients (Z = −2.81, Table 5) and the corresponding 2 year rates were 5.2 and 8.2, respectively (Z = −3.03, Table 5).

Table 6 shows the occurrence of other nonfatal cardiovascular events not reviewed by the Mortality and Morbidity Committee. The Persantine plus aspirin group showed lower incidence of definite intermittent cerebral ischemic attacks and of hospitalization for myocardial infarction as reported by the clinic physician (Z = −3.11 and −3.11, respectively). More patients in the Persantine plus aspirin group than in the placebo group were hospitalized for gastrointestinal disorders, but the difference was not significant (Z = 1.69).

Side effects and other findings. The Persantine plus aspirin group showed the expected side effects, reported by the patients as complaints or by their physicians as problems or reasons for discontinuing drug treatment (Table 7). Side effects included stomach pain, heartburn, nausea, gastrointestinal irritation and gastrointestinal bleeding. For most of these findings, the differences were large and yielded Z values of greater than 3.00. There were also more patients in the Persantine plus aspirin group who complained of headache, a known side effect of dipyridamole (Z = 4.67).

Table 8 gives the percent of patients ever outside given limits for certain biochemical and clinical measurements. Higher proportions of patients in the combination treatment group than in the placebo group showed elevations in serum urea nitrogen, uric acid and creatinine. The drug-placebo differences for serum urea nitrogen and uric acid were highly statistically significant, but increases for individual patients were generally small and not associated with clinical problems. Fewer patients in the Persantine plus aspirin group than in the placebo group had a total serum bilirubin higher than 1.5 mg/dl. More patients in the combination group had a systolic blood pressure less than 100 mm Hg at some point during follow-up. Other changes in systolic and diastolic blood pressure were small. A larger proportion of patients in the Persantine plus aspirin group than in the placebo group had a hematocrit less than 35% at some time during the study.

Subgroup analyses. Early in the study, before any study data were reviewed, the Data Monitoring Committee formulated three subgroup hypotheses, namely, that the Persantine-aspirin combination would have a beneficial effect on the three primary end points in patients at lower risk, that is, in one or more of the three (overlapping) baseline subgroups: a) patients in New York Heart Association functional class I, b) patients with a history of only one myocardial infarction (the qualifying event) at the time of entry

Table 6. Nonfatal Events Reported by Clinic Physicians

	Percent Patients		Z Values
	PR/A	PLBO	PR/A vs. PLBO
Definite de novo congestive heart failure	4.7	3.9	1.10
De novo arrhythmias	2.0	3.0	−1.44
Recurrent arrhythmias	6.5	6 3	0.14
Definite intermittent cerebral ischemic attacks	0 7	2.0	−3 11
Definite peripheral arterial occlusion	0.7	0.7	0.00
Definite intermittent claudication (new)	4 0	3.8	0.27
Definite angina pectoris (new)	28 7	28.8	−0.07
Definite angina pectoris (recurrent)	61 9	60.6	0.52
Cardiovascular surgery	8.5	7 7	0.86
Hospitalization for myocardial infarction	4 4	7.0	−3 11
Hospitalization for gastrointestinal disorder	4.4	3 2	1 69
Any hospitalization	40.0	39 5	0 29

PLBO = placebo group; PR/A = Persantine-aspirin group; vs. = versus.

into the study, and c) patients not under prescription for digitalis at the time of entry into the study. These three subgroups were chosen on the basis of PARIS I data which suggested that Persantine-aspirin might be more effective in those subgroups than in the complementary subgroups.

Class I versus class II patients. In PARIS II, coronary incidence at the end of 1 year of patient follow-up was lower in the Persantine plus aspirin group than in the placebo group for patients who were identified as in functional class I compared with those who were in class II at the time of entry into the study (37% reduction compared with 25% reduction)(Table 9). The Z value for the Persantine plus aspirin versus placebo comparison among class I patients was −2.18. None of the other Persantine plus aspirin versus placebo differences in event rates for class I or class II patients yielded Z values greater than 2.0.

Patients with one infarction versus patients with previous infarction. Larger drug-placebo differences in coronary in-

Table 7. Side Effects

	Percent Patients		Z Values
	PR/A	PLBO	PR/A vs PLBO
Patient complaints			
Stomach pain	14 0	6.6	6.79
Heart burn	9.0	5 7	3.50
Vomiting	2 1	0 8	2.85
Hematemesis, bloody stools and black, tarry stools, or both	2 3	1.4	1.74
Constipation	2.3	1.1	2.63
Dizziness	3.9	3.4	0.86
Headaches	7.8	3 9	4 67
Symptoms reported by physicians as problems			
Hematemesis, bloody stools and black, tarry stools, or both	3.4	3.2	0.39
Symptoms suggestive of peptic ulcer, gastritis or erosion of gastric mucosa	15.2	9.8	4.56
Reason for permanent or temporary discontinuation of study medication			
Stomach pain	5.8	2.9	3.97
Heartburn	2 6	2.0	1.20
Nausea without vomiting	2.6	1 5	2.14
Vomiting	1.2	0.1	3.73
Hematemesis, bloody stools and black, tarry stools, or both	1 5	0.9	1 49
Headaches	2.4	1 2	2 55

PLBO = placebo group; PR/A = Persantine-aspirin group; vs. = versus

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Table 8. Patients Outside Given Limits for Laboratory and Clinical Measurements at Any Follow-up Visit

	Percent Patients		Z Values
	PR/A	PLBO	PR/A vs. PLBO
Measurements made at local clinic at each follow-up visit			
Systolic blood pressure (mm Hg)			
<100	11.0	7.6	3.33
≥140	56.2	56.5	−0.15
≥160	19.9	17.9	1.44
≥180	4.9	4.0	1.30
Diastolic blood pressure (mm Hg)			
<60	4.8	3.8	1.41
≥90	46.1	46.4	−0.21
≥95	20.9	19.8	0.77
≥110	3.1	3.2	−0.12
Percent hematocrit < 35	3.6	2.2	2.37
Central laboratory measurements done annually			
Urea nitrogen ≥ 26 mg/dl	12 1	6.2	5.34
Uric acid ≥ 8.5 mg/dl	22 7	13.6	6.10
Creatinine ≥ 1.4 mg/dl	21.7	19.1	1.69
SGOT ≥ 55 units/ml	10.1	10.6	−0.43
Total bilirubin ≥ 1.5 mg/dl	3.4	5.9	−3 10
Potassium < 3.4 mEq/L	2.6	3.2	−1.02

PLBO = placebo group; PR/A = Persantine-aspirin group; SGOT = serum glutamic oxaloacetic acid transaminase; vs = versus.

cidence at the end of 1 year of patient follow-up and at the end of the study were observed for patients who had only one myocardial infarction compared with those who had had one or more infarctions before the event which made the patient eligible for PARIS II. There was a 34% reduction in the Persantine plus aspirin group compared with the placebo group ($Z = -2.57$) at the end of 1 year of patient follow-up and a 24% reduction at the end of the study ($Z = -2.25$). The Z values for all other drug-placebo comparisons for subgroups defined by number of myocardial infarctions were less than 2.0.

Patients taking versus those not taking digitalis. The largest drug-placebo differences in the subgroups defined a priori were observed for coronary incidence among nonusers of digitalis. The Persantine plus aspirin group was found to have a lower incidence ($Z = -3.45$ for total events and $Z = -3.32$ for first year events)(Table 9). Among users of digitalis (at entry into the study), the differences were small but favored the placebo group.

Role of beta-receptor blockers. During the course of the study in October 1982, it became clear that a large proportion (46%) of the patients enrolled in PARIS II were using beta-receptor blocking agents at entry and the Data Monitoring Committee decided to monitor this subgroup of patients to determine whether the Persantine-aspirin treatment effects were the same whether or not a patient was taking a beta-receptor blocking agent. In the subgroup taking these agents, there was a large reduction in the Persantine plus aspirin group compared with the placebo group in occurrence of all the primary end points (Table 9). For coronary incidence, $Z = -2.97$ at the end of the study and $Z = -3.09$ for first year events. In the complementary group (nonusers of beta-receptor blocking agents), there was a lower incidence in the combination treatment group than in the placebo group only for coronary incidence (overall and 1 year) but the reduction was not as large as for those taking beta-receptor blocking agents (Table 9).

Other subgroups that were not specified a priori were defined by 31 baseline variables and were monitored during the course of the study. None yielded large drug-placebo differences.

Role of time from myocardial infarction to entry into study. The results for two other baseline variables were examined after the study ended and are given in Table 9. Patients were divided into two groups based on time from the qualifying myocardial infarction to the time of entry into the study. The median time of 85 days to entry was used to define the subgroups. Patients enrolled within 85 days of the qualifying myocardial infarction showed somewhat larger treatment differences with respect to coronary incidence than the patients enrolled more than 85 days after the acute event; the largest differences were observed during the second year of follow-up.

Role of presence or absence of Q/QS changes in electrocardiogram. The other subgroups examined were classified by presence or absence of Q/QS changes in the elec-

Table 9. Percent of Events for Baseline Subgroups, Z Values and Percent Difference

	Percent Patients		Z Value	Z Value	Percent Difference†	95% Confidence Limits for Percent Difference	
	PR/A	PLBO	PR/A vs. PLBO	Subgroup Effects*	PR/A vs. PLBO	Lower	Upper
NYHA functional class							
Total death-first year							
Class I (n = 811, 826)§	2.7	4 0	−1.44	−1.35	−33	−60	15
Class II (n = 752, 739)	5.9	5.4	0.37		9	−29	64
Total death-total follow-up							
Class I	4.9	5 8	−0.79	−0.88	−16	−44	28
Class II	9.4	8 9	0.34		6	−23	46
Coronary death-first year							
Class I	1.6	2.9	−1.77	−1.37	−45	−72	8
Class II	4 1	4.2	−0 07		− 2	−40	60
Coronary death-total follow-up							
Class I	3 2	4.1	−0.98	−0.95	−22	−53	29
Class II	6.8	6 5	0.22		5	−29	53
Coronary incidence‡-first year							
Class I	4.3	6.8	−2.18	−0.58	−37	−58	− 4
Class II	6.8	9.1	−1 63		−25	−47	6
Coronary incidence‡-total follow-up							
Class I	7.6	10.3	−1 87	−0 19	−26	−46	2
Class II	10.4	13.4	−1.81		−22	−41	2
Number of myocardial infarctions							
Total death-first year							
One MI (n = 1,319, 1,328)§	3.1	3.8	−1.03	−0.89	−18	−46	21
Two or more MIs (n = 244, 237)	10.2	9 3	0.36		10	−36	90
Total death-total follow-up							
One MI	5.9	6.2	−0.28	−0.26	−5	−29	29
Two or more MIs	13.5	13 5	0 01		0	−36	57
Coronary death-first year							
One MI	2.0	2 8	−1 24	−0.55	−29	−55	20
Two or more MIs	7.0	7.6	−0 27		−8	−52	74
Coronary death-total follow-up							
One MI	3.9	4 3	−0.45	−0.24	−9	−36	33
Two or more MIs	10.2	10 5	−0 11		−3	−43	64
Coronary incidence‡-first year							
One MI	4.5	6 8	−2 57	−0.60	−34	−52	−9
Two or more MIs	11 1	13.9	−0.95		−20	−51	28
Coronary incidence‡-total follow-up							
One MI	7 8	10 3	−2.25	−0 07	−24	−41	−3
Two or more MIs	15.2	19.8	−1.35		−23	−48	13
Digitalis usage							
Total death-first year							
Nonusers (n = 1,319, 1,360)§	3.3	3 8	−0.69	0.01	−13	−42	30
Users (n = 244, 205)	9.4	10 7	−0 46		−12	−50	53
Total death-total follow-up							
Nonusers	5.5	6.3	−0.86	1.01	−13	−35	18
Users	15.6	13.7	0.57		14	−27	79
Coronary death-first year							
Nonusers	2.0	2 9	−1.51	0 73	−31	−58	12
Users	7 4	7.8	−0.17		−5	−51	81
Coronary death-total follow-up							
Nonusers	3.6	4.6	−1 30	1.47	−22	−46	13
Users	12.3	9 8	0 85		26	−26	115
Coronary incidence‡-first year							
Nonusers	4.4	7 4	−3 32	1 81	−41	−57	−19
Users	11.5	10 7	0 25		7	−37	81
Coronary incidence‡-total follow-up							
Nonusers	7 4	11 3	−3.45	2.32	−35	−49	−16
Users	17.2	14.6	0 74		18	−24	81

(continued)

Table 9 *(continued)*

	Percent Patients		Z Value	Z Value	Percent Difference†	95% Confidence Limits for Percent Difference	
	PR/A	PLBO	PR/A vs. PLBO	Subgroup Effects*	PR/A vs. PLBO	Lower	Upper
Beta-receptor blocking drug usage							
Total death-first year							
Nonusers (n = 866, 874)§	6.4	5.5	0 76	−2 39	16	−21	68
Users (n = 697, 691)	1 6	3.6	−2.39		−56	−78	−12
Total death-total follow-up							
Nonusers	9.5	8.7	0.56	−1.30	9	−19	47
Users	4 2	5.5	−1.16		−24	−53	21
Coronary death-first year							
Nonusers	4 4	4.1	0.28	−2.36	7	−32	66
Users	0.9	2.7	−2.65		−67	−87	−22
Coronary death-total follow-up							
Nonusers	6.7	6.1	0.54	−1.56	10	−23	58
Users	2.7	4 2	−1.50		−36	−63	15
Coronary incidence‡-first year							
Nonusers	7.9	9.4	−1 14	−2 02	−16	−39	14
Users	2.6	5.9	−3.09		−56	−75	−25
Coronary incidence‡-total follow-up							
Nonusers	11.7	13.3	−1 02	−1.87	−12	−32	13
Users	5 6	9 8	−2.97		−43	−61	−17
Time from qualifying MI to entry							
Total death-first year							
≤85 days (n = 772, 818)§	4.1	4.4	−0 25	0.23	−7	−41	50
>85 days (n = 791, 747)	4.3	5.0	−0.61		−14	−45	37
Total death-total follow-up							
≤85 days	7.1	7.7	−0.44	−0.47	−8	−35	31
>85 days	7.1	6.8	0.19		4	−28	50
Coronary death-first year							
≤85 days	3.0	3.3	−0 37	0 59	−9	−48	56
>85 days	2.7	3.7	−1.22		−27	−59	24
Coronary death-total follow-up							
≤85 days	4.9	5.5	−0 52	−0.37	−11	−41	36
>85 days	4.9	5.0	−0 02		− 2	−36	54
Coronary incidence‡-first year							
≤85 days	6.0	8.6	−1 99	−0.24	−30	−51	0
>85 days	5.1	7.1	−1 68		−28	−52	6
Coronary incidence‡-total follow-up							
≤85 days	9.2	13.4	−2.67	−1 33	−31	−48	−9
>85 days	8.7	9.9	−0.80		−12	−36	20
Q Wave Changes at Qualifying MI							
Total death-first year							
Q wave changes (n = 1,114, 1,091)§	4.5	4.6	−0.11	0 77	−2	−33	44
No changes (n = 449, 474)	3.6	4 9	−0.97		−27	−61	37
Total death-total follow-up							
Q wave changes	7.7	7.1	0.51	1 34	8	−20	45
No changes	5.6	7 6	−1.24		−26	−55	20
Coronary death-first year							
Q wave changes	2.9	3.2	−0.46	0.80	−9	−44	44
No changes	2.7	4.2	−1.28		−36	−69	28
Coronary death-total follow-up							
Q wave changes	5.2	4.9	0.37	1.31	6	−25	54
No changes	4.2	6.1	−1.29		−31	−61	22
Coronary incidence‡-first year							
Q wave changes	5.8	7.3	−1.42	1.43	−21	−42	9
No changes	4.7	9.1	−2.63		−48	−69	−15
Coronary incidence‡-total follow-up							
Q wave changes	10 0	10.8	−0.66	2 79	−7	−28	18
No changes	6.5	13.9	−3.73		−53	−69	−30

*This Z value is based on a comparison of the PR/A-PLBO difference in the first subgroup with that difference in the second or complementary subgroup. †$\frac{\text{PR/A (\%)} - \text{PLBO (\%)}}{\text{PLBO (\%)}} \times 100$. ‡Coronary death or definite nonfatal myocardial infarction. §Numbers in parentheses are the denominators for PR/A and PLBO groups, respectively. Denominators for three end points and two time-points are the same MI = myocardial infarction; NYHA = New York Heart Association; PLBO = placebo group; PR/A = Persantine-aspirin group; vs. = versus.

trocardiogram that documented the patient's myocardial infarction and eligibility for the study. In those patients with non-Q/QS electrocardiographic evidence of infarction there was a 53% reduction in coronary incidence in the Persantine plus aspirin group compared with the placebo group at the end of the study ($Z = -3.73$). At the end of 1 year of patient follow-up, there was a 48% reduction in the combination treatment group for the patients with non-Q infarcts ($Z = -2.63$). For patients who had Q wave changes in the qualifying electrocardiogram, the drug-placebo percent difference in coronary incidence was −21% at the end of one year and −7% at the end of the study. The corresponding Z values were less than 2.0.

All tests to determine whether the Persantine-aspirin treatment effects in one subgroup were different from the treatment effects in the complementary subgroup were not statistically significant by study criteria (see column 4 of Table 9).

Data Audit Center review. The Data Audit Center, as part of its special review of each case of definite nonfatal myocardial infarction, documented the criteria used by the Mortality and Morbidity Committee to classify each case.

Table 10. Data Audit Center Review of Events Classified as Coronary Incidence by the Mortality and Morbidity Committee

	PR/A	PLBO
I. Number of definite nonfatal myocardial infarctions according to amount of evidence for the classification		
Coronary death	77	82
Q/QS changes with elevated enzymes	27	36
CK-MB and CK elevated	15	21
CK-MB elevated, CK not elevated	1	0
CK elevated	7	9
Other enzymes elevated	4	6
Q/QS changes without elevated enzymes	2	2
CK-MB and CK elevated (no Q/QS changes)	21	33
CK-MB elevated, CK not done (no Q/QS changes)	1	0
CK elevated (no Q/QS changes)	6	9
Other enzymes elevated (no Q/QS changes)	5	12
CK-MB elevated, CK not elevated (no Q/QS changes)	0	8
CK-MB negative, other enzymes elevated (no Q/QS changes)	1	2
Coronary incidence	140	184

II Number of disagreements between Mortality and Morbidity Committee and clinic physician regarding classification of definite myocardial infarction

	Cases Classified as Definite Myocardial Infarction by Mortality and Morbidity Committee but Not by Clinic Physician	
Reported findings	PR/A	PLBO
Q/QS changes with elevated enzymes	0	1
Q/QS changes without elevated enzymes	1	0
CK-MB and CK elevated (no Q/QS changes)	4	7
CK elevated (no Q/QS changes)	3	1
Other enzymes elevated (no Q/QS changes)	2	6
CK-MB elevated, CK not elevated (no Q/QS changes)	0	6
CK-MB negative, other enzymes elevated (no Q/QS changes)	0	1
Total	10	22
Cases Classified as Definite Myocardial Infarction by Clinic Physician but Not by Mortality and Morbidity Committee		
Q/QS findings with elevated enzymes	0	1
Enzymes elevated (no Q/QS changes)	0	3
No enzymes elevated (no Q/QS changes)	1	0
Total	1	4

CK-MB = creatine kinase, MB fraction, PLBO = placebo group; PR/A = Persantine-aspirin group.

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The numbers of cases in each treatment group are given in Table 10, classified by the amount of evidence which supported the diagnosis of myocardial infarction. The strongest evidence to support the classification occurred when there were new Q/QS changes in the electrocardiograms at the time of the clinical onset of a recurrent myocardial infarction and elevations in one or more specific enzymes [creatine kinase (CK)-MB and total CK or total CK alone] or other enzymes as specified in the guidelines followed by the Mortality and Morbidity Committee. Twenty-seven cases in the Persantine plus aspirin group and 36 cases in the placebo group met these criteria (Table 10). The number of cases in the placebo group compared with the combination treatment group was also higher for each of the other categories of evidence. The frequency of disagreements between the clinic physician classification of a nonfatal event and the Mortality and Morbidity Committee classification by category was also determined by the Data Audit Center. In the Persantine plus aspirin group there were disagreements in 10 (7%) of 140 of the cases classified as definite myocardial infarction by the Mortality and Morbidity Committee. In the placebo group there were 22 (12%) of 184. In addition, four placebo cases and one Persantine plus aspirin case were classified as definite myocardial infarction by the clinic physician but not by the Mortality and Morbidity Committee.

The conclusion of the Data Audit Center review of the Mortality and Morbidity Committee procedures was that the classification of nonfatal and fatal events had been conducted according to established, documented guidelines and criteria. The Data Audit Center further concluded that the Mortality and Morbidity Committee was blind with respect to each patient's treatment assignment and that there was no evidence of bias in the classification of events.

Discussion

Effect on coronary incidence and mortality and all cause mortality. At the end of the study, after an average of 23.4 months follow-up, coronary incidence was 24% lower in the Persantine plus aspirin group than in the placebo group. Coronary mortality was 6% lower for the total follow-up period and all cause mortality was 3% lower in the drug group compared with the placebo group. First year life table rates for Persantine plus aspirin patients were 30, 20 and 11 % lower than the rates for patients receiving placebo for coronary incidence, coronary mortality and all cause mortality, respectively. The differences in coronary incidence at 1 year ($Z = -2.65$) and at the end of the study ($Z = -2.57$) were statistically significant by study criteria ($Z = \pm 2.49$). The reduced rates of coronary incidence largely reflected lower rates of definite nonfatal myocardial infarction in the combination treatment group compared with the placebo group.

With this Persantine-aspirin effect on definite nonfatal myocardial infarction, the question arises as to why there was little effect on coronary mortality and no effect on all cause mortality. It is possible that with a longer follow-up period, the Persantine-aspirin effect on nonfatal myocardial infarction would be reflected in lower mortality rates, even after the treatment is discontinued. In the Coronary Drug Project (29), one of the cholesterol-lowering agents (nicotinic acid) showed a significant beneficial effect on nonfatal myocardial infarction but no effect on mortality during the 6 year course of the study. Long-term posttrial follow-up of these patients showed a significant reduction of mortality for patients previously treated with the drug compared with those previously treated with placebo (30). In the present study, the mortality rate was significantly greater in patients enrolled in the study with more than one myocardial infarction, supporting the concept that a nonfatal myocardial infarction will, in time, result in an increased fatality rate.

Low risk versus high risk patients and Q wave versus non-Q wave infarction. In PARIS II, as well as in PARIS I, there was strong evidence that patients with low risk, that is, patients not using digitalis, patients in New York Heart Association functional class I and patients with only one myocardial infarction were more likely to benefit from Persantine-aspirin treatment than patients who were considered at high risk, that is, patients who used digitalis or were in functional class II or had had at least two myocardial infarctions. There was also some evidence that treatment should be started early, that is, patients enrolled within 85 days of the qualifying infarct showed a larger treatment difference than those patients enrolled later. Although, in a statistical sense, the results for patients with a Q wave infarct were not different from those in patients with a non-Q wave infarct as defined on the basis of the qualifying electrocardiogram, there was a strong suggestion that the effect of Asasantine was particularly marked in the non-Q wave group. As Marmor et al. (31) have emphasized, on the basis of their study of 200 patients with acute myocardial infarction, those with a subendocardial myocardial infarction (non-Q wave infarct) compared with those with initial transmural infarction (Q wave infarct) are more susceptible to reinfarction (43 compared with 8%). Early reinfarction in both groups was associated with an increase in mortality of 128%.

Role of beta-blocker agents. Review of the Beta-Blocker Heart Attack Trial results (32) indicated that propranolol prolonged survival primarily in patients who had a Q wave infarct. No mortality differences were observed for patients who had a non-Q wave infarct. In PARIS II, we have noted a larger effect of Persantine and aspirin in the subgroup of patients using beta-receptor blocking agents than in the subgroup who were not using these agents at the time of entry into the study. There was also no evidence of detrimental effects of the use of Persantine and aspirin and beta-

receptor blocking agents together. The results of PARIS II and the Beta-Blocker Heart Attack Trial suggest that there may be an advantage to taking all three of these agents in the first 12 to 24 months after myocardial infarction.

Implication. PARIS II is the first large-scale randomized controlled trial to yield significant positive effects of platelet-active drugs in reducing incidence of recurrent major coronary events, a prespecified primary end point, in patients recovered from myocardial infarction. The design of PARIS II does not permit an assessment of the relative contribution of the two components of the Persantine and aspirin combination to the observed favorable outcome.

Conclusions

1. Coronary incidence (definite nonfatal myocardial infarction plus death due to recent or acute cardiac event) in the Persantine and aspirin group compared with the placebo group was significantly lower by 30% at 1 year of patient follow-up ($Z = -2.65$) and 24% overall ($Z = -2.57$).

2. All cause mortality was similar in the two groups. Coronary mortality (death due to recent or acute cardiac event) was lower in the Persantine and aspirin group but not significantly so—20% at 1 year and 6% overall.

3. In regard to three prior subgroup hypotheses—concerning low risk patients, that is, those with a) only one infarct, b) in New York Heart Association functional class I, or c) not receiving digitalis treatment at baseline—Persantine plus aspirin treatment compared with placebo showed a greater percent reduction in all primary end points for those with these characteristics compared with those without them. The reduction in risk of a coronary event was largest for those not receiving digitalis treatment.

4. A sizable proportion (44%) of patients were receiving a beta-receptor blocking agent at entry and most continued to take this medication during the course of the study. The beneficial effect of Persantine plus aspirin compared with placebo on coronary mortality and coronary incidence tended to be greater for the patients receiving a beta-receptor blocking drug at baseline than for those not receiving this medication. There was no evidence of detrimental effects of the use of Persantine plus aspirin and a beta-receptor blocking drug together.

5. A large difference between Persantine plus aspirin and placebo for coronary incidence at the end of the study was observed for the subgroup of patients whose qualifying myocardial infarction was classified as non-Q wave infarction. The drug-placebo differences for the complementary group were small.

6. Adverse effects of Persantine plus aspirin were infrequent and were similar to those noted in PARIS I, that is, gastrointestinal irritation or bleeding, headache, increase in serum urea nitrogen levels and occurrence of hyperuricemia.

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