

SULFINPYRAZONE IN THE PREVENTION OF SUDDEN DEATH AFTER MYOCARDIAL INFARCTION

THE ANTURANE REINFARCTION TRIAL RESEARCH GROUP

Abstract We report the results of a randomized, double-blind, multicenter trial comparing sulfapyrazone (200 mg four times a day) and a placebo in the prevention of cardiac mortality among 1558 patients followed for an average of 16 months, beginning 25 to 35 days after a documented myocardial infarction.

All but one of the 106 deaths in the group were cardiac; 59 were sudden. The reduction in cardiac mortality at 24 months in the sulfapyrazone group was 32 per cent ($P = 0.058$), and the reduction in sudden death was 43 per cent ($P = 0.041$).

The benefit of sulfapyrazone was attributable en-

tirely to a reduction in sudden death during the second through seventh months after infarction, when there were 35 cardiac deaths in the placebo group and 17 in the sulfapyrazone group ($P = 0.021$); of these deaths, 24 in the placebo group and six in the sulfapyrazone group were sudden cardiac deaths — a sulfapyrazone-induced 74 per cent reduction in the calculated mortality rate ($P = 0.003$).

We conclude that sulfapyrazone prevents sudden cardiac death during the high-risk period shortly after an acute myocardial infarction, but that there is no further apparent effect beyond the seventh month after infarction. (*N Engl J Med* 302:250-256, 1980)

IN September, 1975, we began a double-blind, multicenter clinical trial to assess the efficacy of sulfapyrazone (200 mg four times daily) in reducing cardiac mortality among patients with a recent, documented myocardial infarction. We stopped adding patients to the study on July 31, 1977. The data accumulated during this 23-month period have already been reported; they showed a statistically significant reduction in total cardiac deaths and in sudden deaths, with the reduction in sudden deaths responsible for almost all the benefit achieved.¹

However, the average duration of follow-up was only 8.4 months, and although a benefit of treatment over the first few months was clear, the long-term effects could not be established. The trial was therefore continued to its predetermined end — the study of all

patients receiving therapy for a minimum of one year and a maximum of two years, to assess both the duration of benefit and any hazards of long-term therapy.

The short-term results were disclosed to all investigators and, through them, to the study patients. Without breaking the code, a new informed consent was sought, and all but seven of the patients in the study elected to continue the trial and their original study drugs. The trial ended on August 15, 1978.

METHODS

Eligibility, Observations, and Measurements

The methods of this trial have been reported previously.¹ All criteria for patient eligibility were established before the start of the trial and applied consistently throughout its duration. Observa-

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tions were recorded at follow-up visits that took place in accordance with the predefined schedule. All data collected on dropouts during their earlier participation in the trial were included in the analysis. The survivorship of every eligible patient ever in the study, including all who withdrew, was determined as of August 15, 1978, or after 24 months from entry.

Classification of Deaths

Since there are different causes of cardiac mortality and sulfinpyrazone may affect each cause differently, specific criteria were employed to ensure appropriate classification of deaths. This was done before the inception of the trial, and these criteria were applied consistently throughout, with all decisions made without knowledge of medication received. Categories of cardiac death included "sudden death," "myocardial infarction," and "other cardiac" deaths.¹ Deaths were reviewed and categorized by the appropriate trial committees, including the audit and policy committees.

In accordance with criteria established before the start of the study, all deaths among eligible patients were also classified as analyzable or nonanalyzable.¹ Analyzable deaths formed the basis for the primary analysis of the efficacy of sulfinpyrazone. All nonanalyzable deaths (those not appropriate for analysis of the drug's efficacy) were tabulated separately. Nonanalyzable deaths included those occurring within the first seven days of therapy, those occurring more than seven days after termination of therapy (dropouts), those among patients who did not comply with instructions, and those attributed directly to surgery in which no association could be established with a nonfatal event while the patient was on study treatment.

Procedures and Statistical Methods

Data were recorded on structured forms and submitted directly to the coordinating center. The information on the forms was subjected to a minimum of 10 per cent data verification of patient eligibility by an independent auditing group (faculty members of Columbia University, School of Public Health, Department of Epidemiology). A comprehensive audit of trial procedures was conducted under the direction of faculty members of the Department of Epidemiology, Johns Hopkins University, and later by faculty members of the departments of Preventive Medicine and Biometrics, University of Colorado, to verify the integrity of the execution of the study. In particular, careful audits were made of the data on patients who died during the study and of the data on a random 10 per cent sample of all other patients.

Assessment of efficacy was based on the regression model and life-table method developed by Cox² and extended by Kalbfleisch.³ To compensate, at least in part, for small imbalances in prognosis that arise by chance, the two treatment groups were compared after adjustment for 43 covariates. Since the set of covariates contained many individual covariates related to prognosis rather than only a few that greatly outweighed all the others, two weighted composites were formulated: one for electrocardiographic covariates and one for nonelectrocardiographic covariates. The Cox adjustment for covariates was the primary method of analysis and is the one referred to in the text unless otherwise noted. Additional analyses were undertaken with the methods of Cox (unadjusted), Mantel,⁴ and Breslow.⁵

RESULTS

Trial Subjects and Follow-up

The number of patients entered into this trial was 1629. Without knowledge of the treatment group, the policy committee excluded 71 patients from analysis because they did not meet the criteria of the investi-

gational protocol. Of the remaining 1558 eligible patients, 1143 (73.4 per cent) completed the protocol as planned, and 415 withdrew prematurely from the study for the reasons listed in Table 1. Each category of withdrawal and eligibility was well balanced between the two treatment groups for both frequency of occurrence and reasons for discontinuation.

Table 2 summarizes the principal characteristics of the 1558 eligible patients as they entered the trial; the characteristics include sex, age, selected details of the medical history, anatomic location of the qualifying myocardial infarction as determined by electrocardiographic changes, and relevant electrocardiographic findings at entry into the study. The two treatment groups had a nearly equal distribution of all characteristics, including the incidence of abnormal ventricular rhythm on the entry tracing.

Table 1. Categorization of Patients Entering Drug Trial after Myocardial Infarction.

CATEGORY	PLACEBO GROUP	SULFINPYRAZONE GROUP	TOTAL
Patients entered	816	813	1629
Ineligible patients	33	38	71
Eligible patients	783	775	1558
Completed study	563	580	1143
Withdrew from study	220	195	415
Medical withdrawals	114	88	202
Newly observed	29	29	58
signs and symptoms			
Intercurrent illness	34	27	61
Unacceptable concomitant medication	51	32	83
Nonmedical withdrawals	106	107	213
Failure to follow	22	26	48
appointment schedule			
Refusal of therapy	36	31	67
Administrative and other problems	48	50	98

The average exposure to therapy was 16.4 months for patients receiving sulfinpyrazone and 15.6 months for those receiving a placebo; the combined average was 16.0 months for all patients followed for at least one year. For those patients who withdrew from the study, the corresponding average exposure to therapy was 7.2 months for sulfinpyrazone and 7.6 months for placebo; the combined average is 7.4 months.

Compliance

Drug compliance, measured by means of tablet counts, was determined for the entire study group. Eighty-seven per cent consistently showed a compliance rate of at least 80 per cent (i.e., took at least 80 per cent of prescribed medication). Compliance rates of less than 80 per cent could be explained in most cases by a documented medical reason or some other

Table 2. History and Selected Characteristics of Patients at Entry into Trial.

CHARACTERISTIC	TOTAL		PLACEBO		SULFINPYRAZONE	
	NO.	(%)	NO.	(%)	NO.	(%)
No. of patients	1558		783		775	
Sex						
Male	1345	(86.3)	679	(86.7)	666	(85.9)
Female	213	(13.7)	104	(13.3)	109	(14.1)
Age (yr)						
<55	713	(45.8)	357	(45.6)	356	(45.9)
56-70	845	(54.2)	426	(54.4)	419	(54.1)
Mean	56.6		56.5		56.8	
History						
Myocardial infarction	323	(20.7)	173	(22.1)	150	(19.4)
Angina	517	(33.2)	263	(33.6)	254	(32.8)
Hypertension	507	(32.5)	252	(32.2)	255	(32.9)
Pulmonary embolism	11	(0.7)	6	(0.8)	5	(0.6)
Thrombophlebitis	43	(2.8)	19	(2.4)	24	(3.1)
Stroke	26	(1.7)	12	(1.5)	14	(1.8)
Claudication	63	(4.0)	35	(4.5)	28	(3.6)
Diabetes	169	(10.8)	92	(11.7)	77	(9.9)
Smoking before infarction	1011	(64.9)	510	(65.2)	501	(64.7)
Electrocardiographic findings at first visit						
Ventricular arrhythmia	49	(3.1)	29	(3.7)	20	(2.6)
Electrocardiographically determined locations of acute infarctions*						
Anterior infarction	586	(37.6)	296	(37.8)	290	(37.4)
Inferior infarction	885	(56.8)	439	(56.1)	446	(57.5)
Anterior and inferior infarction	31	(2.0)	12	(1.5)	19	(2.5)
Lateral infarction	33	(2.1)	19	(2.4)	14	(1.8)
Complete or incomplete left bundle-branch block	8	(0.5)	5	(0.6)	3	(0.4)
Nonspecific ST-T wave abnormalities	15	(1.0)	12	(1.5)	3	(0.4)

*Infarct locations as determined at the time of the qualifying myocardial infarction, in contrast to method in previous publication,¹ in which the categorization of patients was based on the electrocardiogram taken at entry into the trial (25 to 35 days after infarction).

valid reason for interruption of therapy. Only 2 per cent of the study group demonstrated less than 80 per cent compliance without a satisfactory explanation.

Compliance among patients receiving sulfapyrazone was also monitored by means of serum levels of uric acid, which decreased to less than 70 per cent of the base-line value in 87 per cent of the patients. Ten

per cent were found to have fluctuating serum uric acid that correlated with a medical explanation or interruption of therapy. Only 3 per cent showed an unexplained lack of reduction in the serum levels of uric acid.

Analyzable Cardiac Mortality

All analyzable deaths among the eligible patients were cardiovascular in nature. Of 106 deaths, 105 were cardiac, and only one was cerebrovascular. The distribution of analyzable deaths between the two treatment groups and among the subgroups of cardiac death is shown in Table 3. The observed reduction in cardiac mortality at 24 months in the sulfapyrazone group was approximately 32 per cent, which borders on conventional levels of statistical significance ($P = 0.058$). The majority of the deaths were sudden, and the major benefit of sulfapyrazone seems to be in reducing sudden deaths significantly; the observed reduction in the sulfapyrazone group was 43 per cent ($P = 0.041$).

Figures 1 and 2 show the life-table cumulative cardiac and sudden-death rates according to treatment group. Also shown is the number of patients observed within each period. The confidence in these curves is related to the number of patients observed during a given period, and hence, in later study periods there is less reliability of interpretation of differences in cumulative death rates. Nevertheless, it is apparent that there is an increasing gap between the mortality curves of the two groups over the first six months or so, after which the differences between the two curves remain reasonably constant.

This is seen more readily in Table 4, which summarizes the observed analyzable deaths according to time intervals (up to six months and thereafter) and according to two classes of death, sudden and nonsudden. The observed mortality rates, which take into account the varying number of patients at risk, are shown, as are the actual number of deaths observed, sudden and nonsudden, for the same periods. The analysis of analyzable deaths included the first seven days of exposure to risk of all eligible patients, even though death within the first seven days was nonanalyzable. Considering that during the first seven days of drug administration, five deaths occurred in the placebo group (three sudden and two from myocardial infarction) and four in the sulfapyrazone group (two sudden and two from infarction), exclusion of the first seven days from the analyses did not significantly affect the statistical analysis of mortality or the P values.

Table 4 compares the first six months with the seven to 24-month period, since the mortality rate in the placebo group decreased sharply as expected after the first six months, and comparable numbers of deaths for a reasonably accurate analysis could be achieved only by combining the data for the seven to

Table 3. Distribution of Analyzable Deaths at 24 Months after Myocardial Infarction.

CAUSE OF DEATH	DRUG GROUP AND NUMBER OF PATIENTS			P VALUE*
	PLACEBO	SULFINPYRAZONE	TOTAL	
All causes	62	44	106	0.076
All cardiac causes	62	43	105	0.058
Sudden death	37	22	59	0.041
Myocardial infarction	18	17	35	†
Other cardiac causes	7	4	11	†
Other cardiovascular causes	0	1	1	†

*Obtained by Cox's method with adjustment for composite covariates.

†Not analyzed.

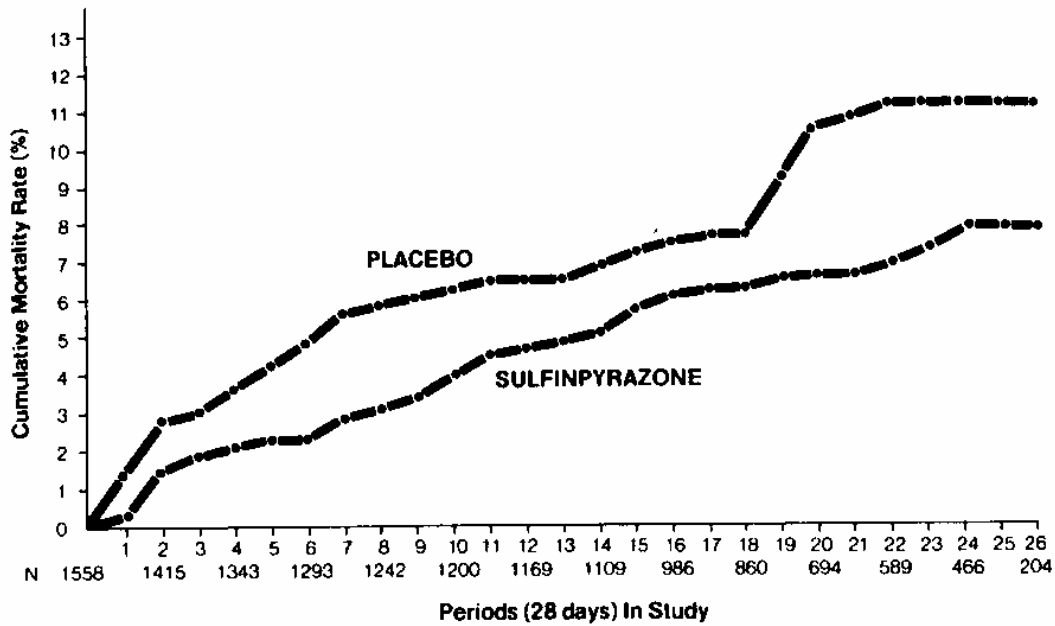


Figure 1. Life-Table Cumulative Mortality Rates for Cardiac Deaths, According to Treatment Group. N denotes number of patients.

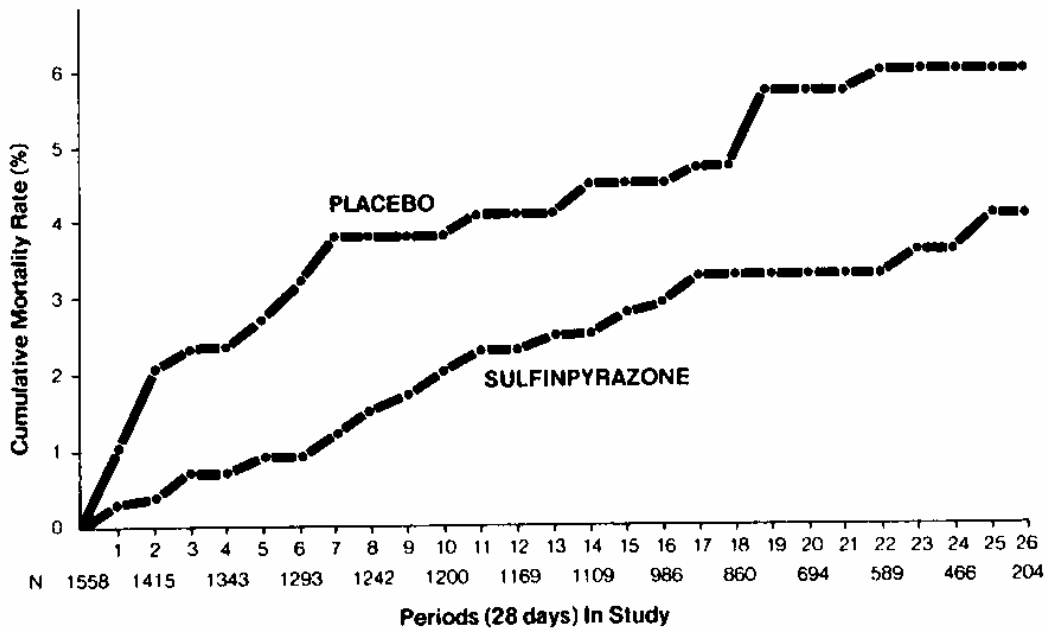


Figure 2. Life-Table Cumulative Mortality Rates for Sudden Deaths, According to Treatment Group. N denotes number of patients.

Table 4. Analyzable Cardiac Deaths (Sudden, Nonsudden,* and All Cardiac) at Intervals after Myocardial Infarction.

CHARACTERISTIC & TREATMENT GROUP	SUDDEN DEATHS		NONSUDDEN DEATHS			ALL CARDIAC DEATHS			
	up to 6 mo	7 to 24 mo	up to 6 mo	7 to 24 mo		up to 6 mo	7 to 24 mo		
Annualized death rates (in %), corrected for length of therapy									
Placebo group	7.0	2.0	3.2	2.1		10.3	4.1		
Sulfinpyrazone group	1.8	2.3	3.2	1.4		5.0	3.7		
No. of analyzable deaths									
Placebo group	24	13	11	14		35	27		
Sulfinpyrazone group	6	16	11	10		17	26		
No. of analyzable deaths and annualized mortality rates (%) for periods after 6 mo									
	7-12 mo	13-18 mo	19-24 mo	7-12 mo	13-18 mo	19-24 mo	7-12 mo	13-18 mo	19-24 mo
Placebo group	5 (1.7)†	7 (3.1)	1 (0.8)	4 (1.3)	6 (2.6)	4 (3.0)	9 (3.0)	13 (5.7)	5 (3.8)
Sulfinpyrazone group	10 (3.2)	4 (1.6)	2 (1.4)	5 (1.6)	4 (1.6)	1 (0.7)	15 (4.8)	8 (3.2)	3 (2.1)

*Includes myocardial infarction and other cardiac deaths.

†Figures in parentheses denote percentages.

24-month period. However, a complete breakdown of the numbers of deaths and mortality rates for the respective six-month periods (seven to 12, 13 to 18, and 19 to 24 months) is also displayed in Table 4.

In the first six-month period, the annualized rate of sudden death in the placebo group was 7.0 per cent, but it was only 1.8 per cent in the sulfinpyrazone group; this 74 per cent reduction was a highly significant difference ($P = 0.003$). Thereafter, the rates of sudden death are comparable in the two groups (2.0 vs. 2.3 per cent). The corresponding rates of nonsudden death were quite similar for the placebo and sulfinpyrazone groups throughout the study.

The significance of the life-table comparisons for sudden or all cardiac deaths either for the first six months or for the entire trial are summarized in Table 5 for the four statistical procedures applied. The results were consistent regardless of the method of analysis employed. Sudden deaths showed a highly significant reduction at six months and a significant reduction for the entire trial. All cardiac deaths, because of the marked decrease in sudden deaths, also showed a highly significant reduction at six months and a borderline significant reduction for the entire two-year period of observation.

One concern that is often raised relates to the concomitant use of beta blockers and their possible influence on the findings of this study. Approximately 36 per cent of trial patients received concomitant beta blockers at one time or another, but their distribution between the two groups was nearly equal (278 of the patients taking placebo, 280 taking sulfinpyrazone).

Nonanalyzable Deaths

Nonanalyzable deaths are summarized in Table 6. They are distributed fairly evenly between the two treatment groups in terms of both frequency and cause of death.

Analysis of All Sudden Deaths

Although this trial was designed to study eligible patients and analyzable events according to predetermined criteria, statistical analyses of other events have also been completed for the entire 24 months of observation: all sudden deaths (analyzable and nonanalyzable) among eligible patients are compared with those among all patients (eligible and ineligible) entered into the trial. The data, treated with four different methods of analysis, are shown in Table 7. Regardless of the category of patient or method of analysis, the reduction in sudden death attributable to sulfinpyrazone during the entire trial is highly significant.

Table 5. P Values for the Major Comparisons among Sudden and Cardiac Analyzable Deaths Six and 24 Months after Myocardial Infarction.

STATISTICAL METHOD	FIRST 6 MO		24 MO	
	SUDDEN DEATHS	ALL CARDIAC DEATHS	SUDDEN DEATHS	ALL CARDIAC DEATHS
Cox (adjusted)	0.003	0.021	0.041	0.058
Cox (unadjusted)	0.003	0.017	0.050	0.061
Breslow	0.001	0.013	0.023	0.044
Mantel	0.001	0.013	0.040	0.045

The reduction in sudden deaths, both analyzable and nonanalyzable, among eligible patients treated with sulfinpyrazone was 68 per cent ($P = 0.004$) at six months, by which time the majority of sudden deaths had occurred. For the entire 24-month observation period, the reduction was 41 per cent. The data for all patients was a reduction of 63 per cent at six months ($P = 0.005$) and 38 per cent at 24 months.

Rehospitalizations

During the trial, there were 1016 rehospitalizations among eligible patients, 554 in the placebo group and 462 in the sulfinpyrazone group ($P \approx 0.005$, which would be exact if each rehospitalization were an independent event). Within the various surgical or medical categories for rehospitalizations, there were no statistically significant differences between drug groups, although medical rehospitalizations were less frequent in the sulfinpyrazone group.

Signs and Symptoms That Emerged during Treatment

Signs and symptoms that emerged after entry into the trial were recorded at each visit according to frequency, severity, and duration. For 21 of the 23 categories described in the initial report, the differences between the two treatment groups in the number of patients reporting such signs and symptoms did not exceed 2 per cent. For the other two categories, thromboembolic events (deep-vein thrombosis, transient cerebral ischemia, stroke, and pulmonary embolism) were reported in 36 patients (5 per cent) of those receiving placebo and only 19 patients (2 per cent) of those receiving sulfinpyrazone; gastrointestinal symptoms were reported in 185 patients (24 per cent) of those in the placebo group, as compared with 214 patients (28 per cent) of those in the sulfinpyrazone group. In total, new signs or symptoms were reported by 84 per cent of the placebo-treated patients and 81 per cent of the sulfinpyrazone-treated patients, with an average experience of 2.8 per patient in the placebo group and 2.9 in the sulfinpyrazone group. None of the observed differences between the two treatment groups were statistically significant, except for thromboembolic events ($P < 0.05$), which favored sulfinpyrazone.

There were no reports of serious side effects associated with sulfinpyrazone. Blood dyscrasias were not reported in either treatment group. A case of renal shutdown in a patient receiving sulfinpyrazone was reported one day after the start of therapy; however, after extensive review of all data, including autopsy data, no cause-and-effect relation to the drug could be established.

The proportion of patients who withdrew from the study as a result of signs and symptoms that emerged during treatment was 3.7 per cent of each treatment group.

Table 8. Distribution between Treatment Groups of Nonanalyzable Deaths after Myocardial Infarction.

CAUSE OF DEATH	TREATMENT GROUP		
	PLACEBO	SULFINPYRAZONE	TOTAL
All causes	23 (10,13)*	20 (10,10)	43 (20,23)
All cardiac causes	16 (8,8)	16 (9,7)	32 (17,15)
Sudden death	9 (4,5)	6 (3,3)	15 (7,8)
Myocardial infarction	6 (4,2)	7 (4,3)	13 (8,5)
Other cardiac causes	1 (0,1)	3 (2,1)	4 (2,2)
Noncardiac causes	7 (2,5)	4 (1,3)	11 (3,8)

*Numbers in parentheses denote deaths during first six months and the subsequent 18 months after myocardial infarction, respectively.

Laboratory Findings

Laboratory studies were carried out to measure hemoglobin, hematocrit, leukocyte count and differential, serum uric acid, alkaline phosphatase, creatinine, potassium, sodium, chloride, glucose, cholesterol, serum aspartate aminotransferase, total bilirubin, blood urea nitrogen, platelet count, and prothrombin and partial thromboplastin time; urinalysis was also done. Except for serum uric acid, laboratory findings were comparable between the two treatment groups and did not deviate significantly from baseline values measured at entry into the study. No abnormal hematologic or urinary findings were associated with sulfinpyrazone therapy.

DISCUSSION

Excluding the "early mortality period" or the first month after myocardial infarction, the highest cardiac mortality rate, about 9 per cent, occurs during the next six months. Cardiac mortality drops sharply from the seventh month after infarction to an annual rate of 3 to 4 per cent for the subsequent four to five years.⁴⁻⁸

More recent studies have confirmed that the risk decreases with time. Cardiac death rates six months after infarction (including the first, high-risk month) have been reported as high as 15 per cent and almost four times the death rates during the subsequent six months. As much as 60 to 80 per cent of the mortality during this first year after infarction has reportedly been sudden cardiac death.⁹⁻¹¹ On the basis of these

Table 7. Statistical Analysis of Sulfinpyrazone versus Placebo in the Prevention of Sudden Death after Myocardial Infarction.

CATEGORY OF PATIENT	STATISTICAL METHOD			
	COX, ADJUSTED	COX, UNADJUSTED	BRESLOW	MANTEL
	P VALUE			
Eligible patients — analyzable events only	0.041	0.050	0.023	0.040
Eligible patients — all events	0.035	0.038	0.034	0.032
All patients — all events	0.032	0.035	0.030	0.028

reports, it has been inferred that the mortality associated with acute myocardial infarction is virtually dissipated after six months and that therapeutic interventions should occur early after the acute event.⁹

The results in the placebo group of this trial are compatible with the existing knowledge of mortality rates and patterns after myocardial infarction — the period of the highest risk was early after the acute event — and the risk decreased substantially with time. Six months after entry into the trial (29 per cent of the average time of observation in this study), 56 per cent of all cardiac deaths in the placebo group and 65 per cent of the sudden deaths in that group had occurred. This indicates that temporal considerations should be emphasized in the interpretation of results of clinical trials studying patients who have recently had myocardial infarctions. This trial was designed with an awareness of these temporal considerations; consequently, patients were recruited 25 to 35 days after the occurrence of a documented myocardial infarction. The patients were, therefore, both relatively homogeneous and at high risk.

The results of this trial have been examined temporally from the time of entry into the study. The cause-specific mortality data indicate that the benefit of sulfinpyrazone in the prevention of all cardiac deaths is greatest during the early high-risk period (zero to six months after entry into the trial) when the majority of deaths occur. Thereafter, differences between treatment groups remain constant until the end of the study, and the adjusted Cox analysis of the total deaths still indicates borderline significance at conventional levels.

Table 3 also gives cause-specific mortality data. It appears that the principal benefit of sulfinpyrazone therapy is in the reduction of sudden cardiac death during the early high-risk period. Even taking into account the limitations of multiple subgroup analysis, the calculated significance ($P = 0.003$) provides persuasive evidence that the major benefit occurs in the early period. This benefit is so striking (a 74 per cent reduction in the rate of sudden death) during the early high-risk period that the overall effect at the end of two years is still substantial (a 43 per cent reduction) and significant ($P = 0.041$).

It is of interest to compare the findings of this study with the one on aspirin by Elwood et al.¹² Their data show that in patients admitted to the study less than six weeks after their myocardial infarction, aspirin resulted in a substantial reduction in mortality as compared with mortality in the placebo group. Although there is no conclusive evidence that aspirin

will have an effect similar to that of sulfinpyrazone during the early period after myocardial infarction, the role of aspirin needs to be studied in future controlled clinical trials.

The original hypothesis on which this study was based was that sulfinpyrazone would prevent platelet-mediated phenomena associated with arterial disease; however, sulfinpyrazone's failure to prevent mortality from myocardial infarction suggests that the drug's prevention of sudden death among those with a recent myocardial infarction is mediated through another mechanism. The finding that sulfinpyrazone reduces the rate of sudden death during the months just after an infarction to the same level encountered after a year and more implies that this agent suppresses the increased incidence of fatal arrhythmias that occur shortly after infarction. A possible explanation, and one under investigation, is that sulfinpyrazone raises the threshold for potentially lethal ventricular arrhythmias arising from areas of myocardial damage associated with severe ischemia.

Regardless of sulfinpyrazone's mechanism of action, which remains for future research to delineate, the results of this trial indicate that the drug is of substantial benefit in preventing sudden cardiac death during a high-risk period in patients who have recently had myocardial infarctions.

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