

Prophylactic antiarrhythmic therapy of high-risk survivors of myocardial infarction: lower mortality at 1 month but not at 1 year

SHELDON H. GOTTLIEB, M.D., STEPHEN C. ACHUFF, M.D., E. DAVID MELLITS, Sc.D.,
GARY GERSTENBLITH, M.D., KENNETH L. BAUGHMAN, M.D., LEWIS BECKER, M.D.,
NISHA C. CHANDRA, M.D., SUSAN HENLEY, B.A., J. O'NEAL HUMPHRIES, M.D.,
CHERYL HECK, PA-C, MARYLU M. KENNEDY, R.N.-C.N.T., MYRON L. WEISFELDT, M.D.,
AND PHILIP R. REID, M.D.

ABSTRACT To determine whether prophylactic antiarrhythmic therapy influences mortality in high-risk patients after acute myocardial infarction, 143 such patients were randomized in a double-blind individually dose-adjusted, placebo-controlled trial an average of 14 ± 7 days after myocardial infarction and followed for 1 year. Patients were judged to be at high risk on the basis of (1) ejection fraction less than 40% ($n = 60$), (2) arrhythmias of Lown class 3 or higher ($n = 26$), or (3) both ($n = 57$). Aprindine was chosen because of its long half-life, few side effects, and antiarrhythmic efficacy. Baseline characteristics in the treatment arms did not differ. Holter-detected arrhythmias were reduced in aprindine-treated patients at 3 months ($p < .001$) and at 1 year ($p < .001$). One patient was lost to follow-up; in the remaining patients 1 year mortality was 20% (28/142; 12 aprindine and 16 placebo). There was no significant difference between the two study arms in overall mortality and sudden death. However, among those who died, median duration of survival was longer in aprindine-treated patients (86 vs 21.5 days) ($p = .04$). Although antiarrhythmic treatment with aprindine of high-risk patients after myocardial infarction does not affect 1 year survival, mortality appears to be delayed; thus there may be a role for short-term treatment before more definitive therapy such as surgery.

Circulation 75, No. 4, 792-799, 1987.

SUDDEN DEATH after hospital discharge following myocardial infarction is thought to be caused by malignant ventricular arrhythmias,¹ and patients with high-grade arrhythmias in the late hospital phase after myocardial infarction have an increased risk of sudden death after hospital discharge.²⁻⁷ Membrane-active antiarrhythmic agents reduce the frequency of ventricular arrhythmias in patients with acute and chronic coronary heart disease,⁸ and these agents have been studied in patients at risk of sudden death after myocardial infarction.^{9, 10} To date, however, no study has shown convincingly that the prophylactic use of antiarrhyth-

mic agents can influence survival after hospital discharge in high-risk survivors of myocardial infarction.¹⁰

This report describes a 1 year, randomized, double-blinded, individually dose-adjusted, placebo-controlled trial to determine whether the administration of a membrane-active antiarrhythmic agent, aprindine,¹¹ influences survival in high-risk survivors of acute myocardial infarction. Aprindine, a tertiary amine with properties similar to those of quinidine and procainamide,¹¹ was chosen as the test drug because it has several major advantages as a prophylactic agent against sudden death after myocardial infarction: (1) it is highly effective against serious ischemia-related arrhythmias; (2) it has a long half-life and predictable pharmacokinetics and may be taken on a twice-daily dosing schedule; (3) the most common side effects, including tremor, nervousness, dizziness and memory impairment, are dose related and readily reversible with dosage titration; and (4) major side effects, agran-

From the Francis Scott Key Medical Center and The Johns Hopkins Hospital, Division of Cardiology, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore.

Supported in part by NHLBI SCOR grant 17655-10.

Address for correspondence: Sheldon H. Gottlieb, M.D., Division of Cardiology, Francis Scott Key Medical Center, 4940 Eastern Ave., Baltimore, MD 21224.

Received Dec. 5, 1985; revision accepted Jan. 8, 1987.

Presented in part at the 58th Scientific Sessions of the American Heart Association, Washington, DC, 1985.

ulocytosis and cholestatic jaundice, are relatively uncommon and reversible upon discontinuation of the drug.

Methods

Population. Between January 1980 and January 1984, patients admitted to the Francis Scott Key Medical Center (formerly the Baltimore City Hospitals) or The Johns Hopkins Hospital within 48 hr of the onset of symptoms of acute myocardial infarction were eligible to be considered for the study. Acute myocardial infarction was defined by the presence of the following: (1) anginal chest, arm, or neck pain lasting longer than 20 min, (2) new Q waves of 0.04 sec or greater duration or new T wave inversion lasting greater than 1 week, and (3) creatine kinase rise to greater than normal.

Inclusion criteria. Eligible patients were invited to participate in the study if they met the following criteria: (1) arrhythmias at 1 week after myocardial infarction of Lown class 3, 4a, or 4b¹² on a 24 hr Holter monitor, or ejection fraction at 1 week after myocardial infarction of less than 40% as determined by cardiac gated blood pool scan, or both high-grade arrhythmias and low ejection fraction; (2) ability and willingness of the patient to give informed consent; and (3) permission of the patient's physician. The study protocol was approved by the institutional committee on human research.

Lown class 3 arrhythmias, i.e., multifocal premature ventricular beats (VPBs), were defined as at least 24 VPBs in 24 hr, 12 each of two different forms, or 12 of one form and a total of 12 of up to 12 other forms. Lown class 4a arrhythmias, i.e., couplets, were defined as at least 12 couplets in 24 hr. Lown class 4b arrhythmias, i.e., ventricular tachycardia, was defined as at least three VPBs in a row at 120 beats/min or greater. Radionuclide ejection fraction was determined in the left anterior oblique view that gave the best separation between the right and left ventricles and was calculated by standard computerized techniques.¹³

Exclusion criteria. Patients were ineligible for the study if they had (1) symptomatic VPBs or ventricular tachycardia with 10 beats or more in a row; (2) persistent second- or third-degree heart block; (3) advanced life-threatening diseases of other organ systems, such as uremia, advanced respiratory disease, cancer or liver failure; (4) complications such as stroke or thromboembolism that required prolonged hospitalization; (5) previously documented hypersensitivity or intolerance to aprindine; or if they (6) were previously treated with membrane-active antiarrhythmic agents such as quinidine, procainamide, or phenytoin; (7) underwent coronary bypass surgery during their primary hospitalization; or (8) were unable to understand or adhere to the study guidelines. There were no age restrictions. Eighty-five percent of the patients who were screened and who met the eligibility criteria and did not have exclusions were enrolled in the study.

Ancillary therapy. There were no restrictions on the use of β -blocking agents, calcium-channel blockers, and antiplatelet or anticoagulation agents. Except for the study drug, membrane-active antiarrhythmic agents were withheld.

Assignment of treatment. Patients were assigned to the aprindine or placebo group by proportional stratified randomization. A balance analysis of the following factors was examined yearly: age, ejection fraction, ventricular arrhythmia class, cardiothoracic ratio of greater than 50% on the 1 week postinfarction chest roentgenogram, and Killip class on admission to the coronary care unit. The randomization list was adjusted yearly by the statistical consultant to keep these factors in balance at both hospitals.

Administration of study drug. After informed consent had been obtained, patients were assigned in double-blinded, randomized fashion to receive aprindine or placebo. Numbered lots of large capsules (25 mg of aprindine/placebo) or small capsules (10 mg of aprindine/placebo) were supplied. A loading dose of 200 mg of aprindine or placebo was given in four divided doses 6 hr apart. If no side effects were noted, the patient was instructed to take two large capsules (50 mg of aprindine/placebo) every 12 hr. The choice of loading and initial maintenance doses was based on previous experience with aprindine at our institution and at other institutions,^{11, 14, 15} which had demonstrated therapeutically effective drug levels in this dosage range. Patients were identified, enrolled, and randomized as soon as possible after the performance and analysis of the initial qualifying 24 hr Holter monitoring and gated blood pool scan, and treatment commenced within 12 hr after consent was given. Before discharge, complete blood counts and liver function tests were obtained. The study drug was to be continued for 1 year after discharge from hospital.

Blinding. The physician investigators, patients, and nursing personnel were blinded to the drug assignment. Drug assignments were known to the statistical consultant and to the technician who measured and reported the drug levels.

One patient who developed severe muscle weakness was thought to have a progressive neuromuscular disorder and the study drug was discontinued; the drug assignment, aprindine, was reported by the statistical consultant to the consulting neurologist. The investigators remained blinded throughout the study, including the study drug dosage adjustment period and the follow-up period (see below).

Individual dosage adjustment of study drug. All patients were seen weekly during the first 16 weeks after randomization to adjust study drug dosage and to monitor for neutropenia, one of the major side effects of aprindine,¹⁶ which occurs most often during the first 4 months of therapy.^{11, 16} Predose blood levels were obtained at each visit and reported by the reference laboratory as a percentage of maximum predicted therapeutic dose. The dose of the drug was adjusted by the investigators until drug levels were at 75% of the predicted maximum dose,¹⁴ at which time a repeat 24 hr Holter electrocardiogram was obtained. Patients in the placebo treatment arm were handled in the same fashion, except that sham levels were reported by the reference laboratory in a pattern that was similar to that seen in patients in the aprindine treatment arm. If Lown class 3, 4a, or 4b arrhythmias were noted in an asymptomatic patient, the drug dose was adjusted upward. Minor complaints compatible with drug intolerance, including tremors, dizziness, and gastrointestinal complaints, were treated by adjusting the level of the study drug or by administering treatment to relieve symptoms. After the initial 16 week period the patient was seen at 3 month intervals, at which time the patient's clinical status was assessed and a 12 lead electrocardiogram, study drug blood levels, liver function tests, complete blood and platelet counts, and a 24 hr Holter electrocardiogram were obtained. The study drug was discontinued for hypersensitivity reaction, persistent toxic symptoms despite reported levels of the agent below 75% of the maximum therapeutic level, neutropenia, or thrombocytopenia. The study drug was also discontinued if patients or their physicians insisted that they stop taking a blinded drug, if they moved from the area and were unable to return for follow-up, or if they underwent open heart surgery or developed severe life-threatening disease such as cerebrovascular accident leading to coma, or severe liver or kidney failure. Patients were referred for coronary angiography and bypass surgery if they had angina pectoris unresponsive to maximal medical therapy with long-acting nitrates, β -blockers, and calcium-channel blockers.

Outcome variables. The primary outcome variable of this study was 1 year mortality from all causes. Secondary outcome variables included sudden death and symptomatic or asymptomatic ventricular tachycardia of 10 or more beats.

Study completion. At the 12 month visit, study drug blood levels and a 24 hr Holter electrocardiogram were obtained and the study drug was discontinued. A repeat 24 hr Holter recording was obtained 2 weeks after discontinuing the study drug.

Compliance. Compliance was assessed by counting capsules at every visit and by randomly obtaining blood samples for drug levels.

Determination of outcome. The status of each randomized patient was determined at 1 year, as was the status of all patients who were not enrolled because they either refused or met one of the exclusion criteria. Outcome was determined while personnel were blinded to the assigned study arm. The status of randomized patients was classified as (1) alive, completed study; (2) sudden death, defined as death within 1 hr of onset of symptoms; (3) cardiac (nonsudden) death, defined as death occurring more than 1 hr after complaints of chest pain or after hospitalization for congestive heart failure; or (4) noncardiac death.

Data analysis. The analysis presented in this article includes all deaths in each treatment arm, whether or not the patient was actively taking the drug at the time of death, according to the intention-to-treat principle.

Univariate analysis on contingent data was performed with the chi-square test and on continuous data with Student's *t* test. The time-dependent nature of treatment failures was examined

with Kaplan-Meier curves¹⁷ and was analyzed with Breslow's test.¹⁸ Differences in the median time to death were tested with the Mann-Whitney U test. Values are expressed as mean \pm 1 SD. All *p* values are two-tailed.

It is apparent that only a marked difference in mortality would have been detected, given the sample size in this study. For a projected mortality in the control group of 25% to 30%, and given *p* < .05 and $\beta = .20$, a reduction in mortality in the treatment arm to 10% to 12% would have been required.¹⁹

Results

A total of 143 patients were randomized, 71 patients to aprindine and 72 to placebo. Their mean age was 61 ± 11 years (range 31 to 87) and 66% were men. There were no significant differences between the treatment arms in the baseline characteristics known to be important prognostic indicators in postinfarction patients^{6, 7} (table 1) nor in drug treatment or smoking status after randomization (table 2). Patients in both groups were randomized and treatment was begun with the study drug an average of 14 days (14 ± 6 aprindine, 14 ± 8 placebo) after myocardial infarction. Twenty-four percent of patients in the aprindine group withdrew because of side effects or because they or their physicians

TABLE 1
Baseline characteristics of patients assigned to aprindine and placebo^A

	Aprindine (n = 71)	Placebo (n = 72)
Age (yr)	60 \pm 12 (31–81)	62 \pm 10 (43–87)
Male	42	53
EF (GBPS)	35 \pm 11% (15–69)	34 \pm 12% (14–75)
Lown class ^B		
1–2	30	30
3	15	16
4a	15	11
4b	11	15
Prior MI	29	33
Max. Killip class		
1–2	50	50
3–4	21	22
CTR	0.52 \pm 0.05 (0.43–0.63)	0.53 \pm 0.06 (0.41–0.70)
CK peak (IU/liter)	1178 \pm 925	1239 \pm 1197
Type MI		
Non-Q wave	29	26
Q-wave infarction	42	46
Location		
Indeterminate	5	7
Anterior	38	44
Inferior	24	16
Lateral	4	5
Ever smoked		
Yes	56	53

EF = ejection fraction; GBPS = gated blood pool scan; MI = myocardial infarction; CTR = cardiothoracic ratio; CK = creatine kinase.

^A*p* = NS.

^BA modified Lown class was used. See text.

TABLE 2
Comparability of drug treatment and smoking status after enrollment^A

	Aprindine (n = 71)	Placebo (n = 72)
Treatment with		
Antiplatelet agents	24	25
β -Blockers	38	29
Digitalis	28	26
Diuretics	50	56
Nitrates	59	59
Cigarette smoker	20	17

^Ap = NS.

insisted that they stop taking a blinded drug, compared with 13% of patients in the placebo group ($p = \text{NS}$). Reasons for stopping the study drug are detailed in table 3. One patient in the aprindine group moved to another state after 3 months and could not be traced; she was not included in the analysis of mortality. One year follow-up was obtained on all other patients.

Antiarrhythmic efficacy of drug. Although there was no baseline difference between treatment arms in ventricular arrhythmias, aprindine treatment resulted in a decrease in Lown class arrhythmias at 3 months ($p < .001$) and 12 months ($p < .001$) after initiating treatment compared with placebo (table 4). Among the 60 patients enrolled with an ejection fraction under 40% with arrhythmias of Lown class 2 or less, 75% (15/20) of the aprindine-treated patients who achieved a drug level of 75% of maximum predicted therapeutic level remained in class 1 or 2 on the 24 hr Holter recording obtained when the patient reached therapeutic level, compared with 41% (9/22) of the placebo-treated patients ($p = .05$) tested when their sham levels were reported at 75% of maximum predicted therapeutic level. Among the 83 patients enrolled with arrhythmias of Lown class 3 or higher (57 with an ejection fraction under 40% and 26 with an ejection fraction of 40% or greater, 43% (12/28) of the aprindine-treated patients who achieved a drug level of 75% of maximum predicted therapeutic level showed a decrease in their arrhythmia class on the 24 hr Holter recording to Lown class 1 or 2, compared with only 3% (1/34) of the placebo-treated patients ($p < .001$) tested when their sham levels were reported at 75% of maximum predicted therapeutic level.

Mortality. There was no significant difference between treatment arms for total deaths ($p = .31$) or sudden deaths ($p = .09$) (figure 1). However, among patients who died from all causes, the median duration of survival was longer in the aprindine-treated patients

(86 days) than in the placebo-treated patients (21.5 days) ($p = .04$). Fifty percent (8/16) of all deaths among patients in the placebo treatment arm occurred by day 18 after randomization, whereas the first death in a patient in the aprindine treatment arm occurred on day 29 in a patient recovering from bypass surgery several days after the drug had been discontinued. The pattern of deaths by month after randomization shows a significant difference in mortality during the first month, when only 8% (1/12) of all deaths in the aprindine arm occurred compared with 56% (9/16) of all deaths in the placebo arm ($p = .02$).

When the data are censored so that only patients who were actively taking the study drug are considered, there is also no significant difference between treatment arms in mortality at 1 year. Among patients who died of all causes, the median duration of survival was longer among patients in the aprindine arm (64 days) than in the placebo arm (8.5 days) ($p < .05$); the first death in a patient actively taking aprindine occurred on day 47 after randomization.

There was no difference in mortality within the subgroups of both treatment arms that entered the study with an ejection fraction less than 40%, with arrhythmias of Lown class 3 or greater, or with both (table 5). The mean ejection fraction of the patients who died in the two treatment arms was identical (aprindine [$n = 12$], ejection fraction = $31 \pm 7\%$; placebo [$n = 16$], ejection fraction = $31 \pm 8\%$).

Drug levels. Aprindine levels were maintained at an average of 70% of the predicted maximum therapeutic

TABLE 3
Reasons for stopping study drug^A

	Aprindine (n = 71)	Placebo (n = 72)
Died while taking study drug	7	10
Coronary artery bypass surgery	11	4 ^B
Symptomatic ventricular tachycardia or asymptomatic ventricular tachycardia ≥10 beats	3	5
Side effects attributed to study drug	11	6
Patient refused to stay on blinded drug or physician insisted patient stop drug	6	3
Moved away	1	0
Other (CVA, cancer)	2	1

CVA = cerebrovascular accident.

^Ap = NS.

^BAn additional patient underwent bypass surgery after being resuscitated from ventricular tachycardia/fibrillation; a total of 11 aprindine- and five placebo-treated patients underwent bypass surgery ($p = .51$, NS).

TABLE 4**Effect of study drug on Lown class arrhythmia as determined by 24 hr Holter monitoring**

Time after MI Holter obtained ^B	Lown class arrhythmias ^A				p value ^C
	Aprindine arm	(n)	Placebo arm	(n)	
1 wk (prerandomization)	2.7 ± 1.5	(71)	2.7 ± 1.6	(72)	NS
3 mo	2.3 ± 1.6	(44)	3.3 ± 1.3	(51)	<.001
12 mo	1.9 ± 1.3	(30)	3.4 ± 1.4	(36)	<.001

^AA modified Lown scoring system was used (see text).^BAll surviving patients had a Holter recording at 3 and 12 months; only patients who tolerated a dose of the study drug that gave a level of ≥75% of maximum predicted had a "therapeutic level" Holter recording. See text.^CLown class was treated as a continuous measure and classes 4a and 4b were grouped together to simplify the analysis; differences between treatment arms were tested with Student's *t* test.

level over the 1 year of treatment. There was no significant difference in the average drug levels for patients who survived (69%) or died (74%), and the average levels, the maximum levels, and the last recorded levels were not different.

Surgical revascularization. A total of 16 patients un-

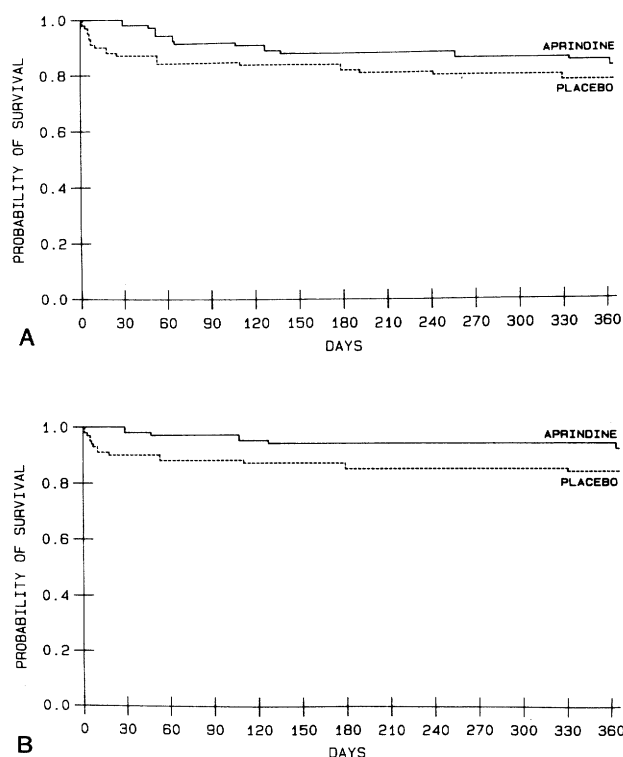


FIGURE 1. Probability of remaining free of death from all causes (A) and from sudden death (B) as a function of time, for aprindine and placebo treatment arms (Kaplan-Meier curves). The probability of survival at 1 year was not significantly different between treatment arms for death from all causes (A) ($p = .31$) or for sudden death (B) ($p = .09$). At 1 year, 83% (58/70) of patients in the aprindine arm were alive, with 46% (32/70) still taking the study drug and 7% (5/70) having died suddenly. In the placebo arm, 78% (56/72) of patients were alive at 1 year, with 57% (41/72) of patients still taking the study drug and 15% (11/72) having died suddenly.

derwent coronary artery bypass graft surgery during the 1 year follow-up, 11 treated with aprindine and five with placebo ($p = .51$, NS). Bypass surgery was a study end point in 15 patients (11 treated with aprindine and four with placebo). Ventricular fibrillation was a study end point in one placebo-treated patient who, after being resuscitated, later underwent bypass surgery (see table 3). The 11 aprindine-treated patients underwent surgery at a median time of 71 days (range 17 to 250) after randomization, compared with a median time of 89 days (range 34 to 269) for the five placebo-treated patients ($p = NS$).

Mortality in concurrent unenrolled reference patients.

The 1 year mortality among 150 consecutive patients with documented myocardial infarction who did not meet entry criteria because their ejection fraction was 40% or greater and because they did not have high-grade arrhythmias was 5%.

Discussion

Malignant ventricular arrhythmias are the proximate cause of death in most patients who die suddenly after hospital discharge after an acute myocardial infarction.^{1, 20} Membrane active antiarrhythmic agents appear to reduce the risk of sudden death in patients who have been resuscitated from ventricular fibrillation²¹ and also prophylactically reduce the incidence of ven-

TABLE 5**Deaths by category of enrollment in study**

Enrollment category	Aprindine		Placebo	
	No. of deaths/No. enrolled	%	No. of deaths/No. enrolled	%
Ejection fraction <40%	5/29	17	8/30	27
Lown class arrhythmia ≥3	1/15	7	2/11	18
Both of the above	6/26	23	6/31	19

tricular fibrillation in patients within a few hours of the onset of acute myocardial infarction.^{10, 22} However, no clinical trial of the use of membrane-active antiarrhythmic agents in high-risk patients after acute myocardial infarction has shown a beneficial effect on mortality. Of the seven large randomized trials including more than 100 patients, none showed a beneficial effect on mortality and several showed a trend toward a detrimental effect.^{23–29} In the most recently reported large randomized trial of the use of mexiletine, a membrane-active antiarrhythmic agent, in high-risk patients after acute myocardial infarction with 1 year follow-up,²⁹ no early or late benefit was seen. There was a trend toward an increased mortality in the intervention arm despite effective suppression of arrhythmias.

Our study was designed to determine whether the membrane-active antiarrhythmic agent, aprindine, a highly effective drug with a long half-life and properties similar to those of procainamide and quinidine,^{11, 15} would reduce the risk of death in high-risk survivors of acute myocardial infarction. Our study differed from previously reported studies of this question in several important features: (1) High-risk patients were selected. Mortality from all causes in the placebo arm of other studies ranged from only 4.8%²⁷ at 1 year to 11.6% at 6 months.²⁵ Mortality in the placebo arm of our study was 22% (16/72) at 1 year and 18% at 6 months. In no other reported study was ejection fraction evaluated routinely, whereas in our study all patients had their ejection fraction determined by gated blood pool scanning and 85% (121/143) of patients had an ejection fraction less than 40%. (2) Study drug dose was individually adjusted. No other double-blinded study individually adjusted the dose of the study drug so that blood levels were in a range known to be effective in reducing sudden death. The pharmacokinetics of aprindine are predictable and the levels we achieved with a twice-daily dosing schedule have been shown to be effective in improving survival in a sample of patients with ventricular tachycardia or fibrillation.¹⁴ (3) A drug highly effective against lethal ventricular arrhythmias was used. Aprindine is highly effective against lethal ventricular arrhythmias and has been shown to be effective in a group of patients with symptomatic ventricular tachycardia or fibrillation in improving the proportion of patients remaining alive and asymptomatic.¹⁴ It appears to be among the most effective drugs available for treatment of lethal ventricular arrhythmias.⁹

Although some previously reported studies of the prophylactic use of membrane-active antiarrhythmic

agents in survivors of acute myocardial infarction have been criticized because high-grade arrhythmias were not one of the criteria for enrollment,¹⁰ an ejection fraction of less than 40% after acute myocardial infarction has repeatedly been shown to be a major risk factor for death after discharge from hospital; most of these patients die suddenly.^{30, 31} Malignant ventricular arrhythmias are thought to be the cause of death in most of these patients,¹ perhaps because extensive scar or ventricular aneurysm may form an anatomic substrate responsible for the generation of malignant arrhythmias by creating reentry circuits, or may extend the vulnerable period when an ectopic beat with a critical amplitude and timing may trigger ventricular fibrillation.³² In the canine preparation,³³ sustained monomorphic ventricular tachycardia can be induced reproducibly by electrical stimulation 2 weeks after experimental myocardial infarction and the likelihood of inducibility is strongly correlated with the size of the infarct. Among our patients enrolled because of an ejection fraction under 40%, without high-grade arrhythmias, the prevalence of high-grade arrhythmias increased over time, and this increase was greatest in the placebo-treated patients. By the time the first follow-up 24 hr ambulatory electrocardiogram was performed, half the deaths in the placebo arm had already occurred. Thus an ejection fraction of less than 40% after myocardial infarction identifies a group of patients who are likely to manifest high-grade arrhythmias on follow-up examinations. Marked natural variability in frequency of arrhythmias has been noted previously by other investigators,³⁴ and an increase in frequency and complexity of ventricular ectopic beats in the first 1 to 6 months after acute myocardial infarction has been shown.^{3, 35}

Our study indicates that over a 1 year period the prophylactic administration of an effective membrane-active antiarrhythmic agent, aprindine, given in a randomized, double-blind, individually dose-adjusted, placebo-controlled trial to high-risk survivors of acute myocardial infarction appears to reduce mortality in the first month after randomization and may prolong survival by approximately 2 months in those patients who later die; however, mortality at 1 year does not appear to be affected. This apparent reduction in early mortality appears to be due in large part to the difference in the incidence of early sudden death between the two groups: half of the deaths (8/16) in the placebo arm occurred by day 18 after randomization and seven of these were sudden. The first death among the aprindine-treated patients did not occur until day 29; this was a patient who died suddenly after bypass surgery

several days after withdrawal of the drug. The first death in a patient actively taking aprindine did not occur until day 47 after randomization. Fifty percent of deaths in the aprindine arm occurred by day 65, and only two of six were sudden.

Although more aprindine-treated patients underwent coronary artery bypass graft surgery (11 aprindine vs five placebo; see table 3), this difference was not significant ($p = .51$). The first bypass graft surgery performed on an aprindine-treated patient was at 17 days after randomization; at that time, seven deaths (six of them sudden) had already occurred in the placebo group. To control for the possibility that differences in clinical outcome after coronary bypass graft surgery may have accounted for the apparent differences in mortality between the aprindine and placebo treatment arms, we reanalyzed the data, censoring the data at the time of bypass graft surgery. The results of this censored analysis show no difference between the two treatment arms in death from all causes at 365 days ($p = .22$) or at 120 days ($p = .10$). However, the censored analysis does show a significant difference between the two treatment arms in mortality due to sudden death: when the data are censored, among patients who did not undergo bypass graft surgery there are four sudden deaths in the aprindine arm and 11 sudden deaths in the placebo arm. There is a significant difference in mortality due to sudden death at 1 year ($p = .048$, Breslow's test) and at 120 days ($p = .027$, Breslow's test). It is possible that some of the placebo-treated patients who died suddenly soon after randomization may have been candidates for coronary artery bypass surgery had they survived for several more weeks.

The suggested decrease in mortality in the aprindine treatment arm during the first month after randomization is noteworthy. It has been shown that mortality is highest in the first few months after myocardial infarction^{1–3, 5, 7, 36–38} and then progressively decreases.² Moss *et al.*³ showed that frequent ventricular ectopic beats were associated with increased mortality only during the first 4 months after myocardial infarction. It thus seems reasonable to expect that the greatest benefit of antiarrhythmic therapy would be seen in the first few months after myocardial infarction. This has not been demonstrated, however, in prior studies of prophylactic antiarrhythmic therapy after myocardial infarction. Many studies have enrolled patients after myocardial infarction for a variable period of time, approaching 2 months in some.^{10, 39} This is beyond the period of highest mortality, and thus the power to demonstrate a difference between treatment arms may be reduced.

This is in contrast to trials of the prophylactic use of β -blocking agents. In the Norwegian multicenter trial of timolol after myocardial infarction, a progressively increasing difference in mortality due to cardiac death was seen throughout the study follow-up period.⁴⁰

The difference in mortality from all causes at 1 year between the aprindine arm and the placebo arm (17% vs 22%) was small, and the statistical power to detect a significant difference is limited by the sample size. To show a significant difference between treatment arms for death from all causes with $p < .05$ and a beta error of 20%, more than 1000 such high-risk patients in each treatment arm would have been necessary.¹⁹

The characteristics of an ideal antiarrhythmic agent for prophylactic use against sudden death after discharge of survivors of acute myocardial infarction include high efficacy in suppressing ventricular arrhythmias, a long half-life, and tolerable side effects.⁹ At the time this study was initiated, aprindine appeared to be one of the most promising agents available. In our study, the drug appeared to be an effective antiarrhythmic agent with tolerable side effects. Although central nervous system side effects, usually weakness and tremor, were seen in 15% of patients treated with aprindine, they were usually controlled by reducing the dose. Only one case of significant neutropenia was seen and this promptly resolved when the drug was discontinued. The long half-life of the drug allowed it to be taken on a convenient 12 hr dosing schedule and compliance was good. No suggestion of exacerbation of ventricular arrhythmias was seen despite high drug levels achieved in some patients. The prolongation of survival associated with aprindine treatment in this study cannot necessarily be extrapolated without qualification to the use of other antiarrhythmic agents. The primary advantage of aprindine may be its long half-life and the relative ease with which therapeutic drug levels with tolerable side effects may be achieved.¹⁴ Aprindine may have other properties that make it particularly effective in reducing sudden death in patients in the early postinfarction period.

Finally, it has been demonstrated that patients with depressed ejection fraction and triple-vessel disease benefit from bypass surgery.⁴¹ It is among this group of patients, however, that the highest early mortality is seen.^{36, 42} Our results suggest that an effective strategy for high-risk patients may be to prolong hospitalization and initiate treatment by the aggressive use of β -blockers,⁴⁰ calcium-channel blockers,⁴³ and a membrane-active antiarrhythmic agent; this strategy may prolong survival until the patient's suitability for surgery may be assessed.

We thank Rosemary Baumgartner and Clayton Kallman for assistance with the statistical analysis and Joyce Rathell for assistance in the preparation of the manuscript.

References

- Moss AJ, DeCamilla J, Davis H: Cardiac death in the first 6 months after myocardial infarction: potential for mortality reduction in the early posthospital period. *Am J Cardiol* **39**: 816, 1977
- Mukharji J, Rude RE, Poole WK, Gustafson N, Thomas LJ Jr, Strauss HW, Jaffe AS, Muller JE, Roberts R, Raabe DS Jr, Croft CH, Passamani E, Braunwald E, Willerson JT, MILIS Study Group: Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol* **54**: 31, 1984
- Moss AJ, DeCamilla JJ, Davis HP, Bayer L: Clinical significance of ventricular ectopic beats in the early posthospital phase of myocardial infarction. *Am J Cardiol* **39**: 635, 1977
- Taylor GJ Jr, Humphries JO, Pitt B, Griffith LSC, Achuff SC: Complex ventricular arrhythmias after myocardial infarction during convalescence and follow-up: a harbinger of multi-vessel coronary disease, left ventricular dysfunction and sudden death. *Johns Hopkins Med J* **149**: 1, 1981
- Olson HG, Lyons KP, Troop P, Butman SM, Pisters KM: Prognostic implications of complicated ventricular arrhythmias early after hospital discharge in acute myocardial infarction: a serial ambulatory electrocardiography study. *Am Heart J* **108**: 1221, 1984
- Multicenter Postinfarction Research Group: Risk stratification and survival after myocardial infarction. *N Engl J Med* **309**: 331, 1983
- Bigger JT Jr, Heller CA, Wenger TL, Weld FM: Risk stratification after acute myocardial infarction. *Am J Cardiol* **42**: 202, 1978
- Lovell RRRH: Arrhythmia prophylaxis: long-term suppressive medication. *Circulation* **51/52**(suppl III): III-236, 1975
- Woosley RL, Roden DM, Duff HJ, Oates JA: Selection of an antiarrhythmic drug for a sudden-death-prevention trial. *Am Heart J* **103**: 737, 1982
- Furberg CD: Effect of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol* **52**: 32C, 1983
- Zipes DP, Elharrar V, Gilmour RF Jr, Heger JJ, Prystowsky EN: Studies with aprindine. *Am Heart J* **100**: 1055, 1980
- Lown B, Wolf M: Approaches to sudden death from coronary heart disease. *Circulation* **44**: 130, 1971
- Burow RD, Strauss HW, Singleton R, Pond M, Rehn T, Bailey IK, Griffith LC, Nickoloff E, Pitt B: Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging. *Circulation* **56**: 1024, 1977
- Vlay SC, Kallman CH, Reid PR: The utility of aprindine blood levels in the management of ventricular arrhythmias. *J Am Coll Cardiol* **5**: 738, 1985
- Greene HL, Reid PR, Schaeffer AH: Prolongation of cardiac conduction times by intravenous aprindine in man. *Am J Cardiol* **42**: 1002, 1978
- van Leeuwen R, Meyboom RHB: Agranulocytosis and aprindine. *Lancet* **2**: 1137, 1976
- Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* **53**: 457, 1958
- Breslow N: A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. *Biometrika* **57**: 579, 1970
- Lachin JM: Introduction to sample size determination and power analysis for clinical trials. *Controlled Clin Trials* **2**: 93, 1981
- Baum RS, Alvarez H III, Cobb LA: Survival after resuscitation from out-of-hospital ventricular fibrillation. *Circulation* **50**: 1231, 1974
- Myerburg RJ, Briesse FW, Conde C, Mallon SM, Libberthson RR, Castellanos A Jr: Long-term antiarrhythmic therapy in survivors of prehospital cardiac arrest. *JAMA* **238**: 2621, 1977
- Lie KI, Wellens HJ, van Capelle FJ, Durrer D: Lidocaine in the prevention of primary ventricular fibrillation: a double-blind, randomized study of 212 consecutive patients. *N Engl J Med* **291**: 1324, 1974
- Collaborative Group: Phenytoin after recovery from myocardial infarction. *Lancet* **2**: 1055, 1971
- Peter T, Ross D, Duffield A, Luxton M, Harper R, Hunt D, Sloman G: Effect on survival after myocardial infarction of long-term treatment with phenytoin. *Br Heart J* **40**: 1356, 1978
- Hugenholtz PG, Hagemeyer F, Lubsen J, Glazer B, VanDurme JP, Bogaert MG: One year follow-up in patients with persistent ventricular dysrhythmias after myocardial infarction treated with aprindine or placebo. In Sandoe E, Julian DG, Pell JW, editors: Management of ventricular tachycardia: role of mexiletine. Amsterdam, 1978, Excerpta Medica, pp 572-578
- Bastian BC, Macfarlane PW, McLaughlan JH, Ballantyne D, Clark R, Hillis WS, Rae AP, Hutton I: A prospective randomized trial of tocainide in patients following myocardial infarction. *Am Heart J* **100**: 1017, 1980
- Chamberlain DA, Julian DG, Boyle DM, Jewitt DE, Campbell RWF, Shanks RG: Oral mexiletine in high-risk patients after myocardial infarction. *Lancet* **2**: 1324, 1980
- Ryden L, Arman K, Conradson TB, Hofvendahl S, Mortensen O, Smedgard P: Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction. *Am Heart J* **100**: 1006, 1980
- IMPACT Research Group: International mexiletine and placebo antiarrhythmic coronary trial. I. report on arrhythmia and other findings. *J Am Coll Cardiol* **4**: 1148, 1984
- Schulze RA, Strauss HW, Pitt B: Sudden death in the year following myocardial infarction. *Am J Med* **62**: 142, 1977
- Taylor GJ, Humphries JO, Mellits ED, Pitt B, Schulze RA, Griffith LSC, Achuff SC: Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction. *Circulation* **62**: 960, 1980
- Winfree AT: Sudden cardiac death: a problem in topology. *Sci Am* **248**(5): 144, 1983
- Garan H, Ruskin JN, McGovern B, Grant G: Serial analysis of electrically induced ventricular arrhythmias in a canine model of myocardial infarction. *J Am Coll Cardiol* **5**: 1095, 1985
- Michelson EL, Morganroth J: Spontaneous variability of complex ventricular arrhythmias detected by long-term electrocardiographic recording. *Circulation* **61**: 690, 1980
- Friedman LM, Byington RP, Capone RJ, Furberg CD, Goldstein S, Lichstein E: Effect of propranolol in patients with myocardial infarction and ventricular arrhythmia. *J Am Coll Cardiol* **7**: 1, 1986
- Olson HG, Lyons KP, Troop P, Butman S, Pisters KM: The high-risk acute myocardial infarction patient at 1-year follow-up: identification at hospital discharge by ambulatory electrocardiography and radionuclide ventriculography. *Am Heart J* **107**: 358, 1984
- Multicentre International Study: Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *Br Med J* **3**: 735, 1975
- Davis HT, DeCamilla J, Bayer LW, Moss AJ: Survivorship patterns in the posthospital phase of myocardial infarction. *Circulation* **60**: 1252, 1979
- Bigger JT Jr: Patients with malignant or potentially malignant ventricular arrhythmias: opportunities and limitations of drug therapy in prevention of sudden death. *J Am Coll Cardiol* **5**: 23B, 1985
- Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* **304**: 801, 1981
- Hammermeister KE, DeRouen TA, Murray JA, Dodge HT: Effect of aortocoronary saphenous vein bypass grafting on death and sudden death. *Am J Cardiol* **39**: 925, 1977
- Vlay SC, Reid PR, Griffith LSC, Kallman CH: Relationship of specific coronary lesions and regional left ventricular dysfunction to prognosis in survivors of sudden cardiac death. *Am Heart J* **108**: 1212, 1984
- Gerstenblith G, Ouyang P, Achuff SC, Bulkley BH, Becker LC, Mellits ED, Baughman KL, Weiss JL, Flaherty JT, Kallman CH, Llewellyn M, Weisfeldt ML: Nifedipine in unstable angina. *N Engl J Med* **306**: 885, 1982

**Prophylactic antiarrhythmic therapy of high-risk survivors of myocardial infarction:
lower mortality at 1 month but not at 1 year.**

S H Gottlieb, S C Achuff, E D Mellits, G Gerstenblith, K L Baughman, L Becker, N C Chandra, S Henley, J O Humphries and C Heck

Circulation. 1987;75:792-799

doi: 10.1161/01.CIR.75.4.792

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 1987 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/75/4/792>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>