EFFECT OF THE ANTIARRHYTHMIC AGENT MORICIZINE ON SURVIVAL AFTER MYOCARDIAL INFARCTION

THE CARDIAC ARRHYTHMIA SUPPRESSION TRIAL II INVESTIGATORS*

Abstract *Background.* The Cardiac Arrhythmia Suppression Trial (CAST) tested the hypothesis that the suppression of asymptomatic or mildly symptomatic ventricular premature depolarizations in survivors of myocardial infarction would decrease the number of deaths from ventricular arrhythmias and improve overall survival. The second CAST study (CAST-II) tested this hypothesis with a comparison of moricizine and placebo.

Methods. CAST-II was divided into two blinded, randomized phases: an early, 14-day exposure phase that evaluated the risk of starting treatment with moricizine after myocardial infarction (1325 patients), and a long-term phase that evaluated the effect of moricizine on survival after myocardial infarction in patients whose ventricular premature depolarizations were either adequately suppressed by moricizine (1155 patients) or only partially suppressed (219 patients).

Results. CAST-II was stopped early because the first 14-day period of treatment with moricizine after a myocardial infarction was associated with excess mortality (17 of 665 patients died or had cardiac arrests), as compared with no treatment or placebo (3 of 660 patients died or had cardiac arrests); and estimates of conditional power indicated that it was highly unlikely (<8 percent chance) that a survival benefit from moricizine could be observed if the trial were completed. At the completion of the long-term phase, there were 49 deaths or cardiac arrests due to arrhythmias in patients assigned to moricizine, and 42 in patients assigned to placebo (adjusted P = 0.40).

Conclusions. As with the antiarrhythmic agents used in CAST-I (flecainide and encainide), the use of moricizine in CAST-II to suppress asymptomatic or mildly symptomatic ventricular premature depolarizations to try to reduce mortality after myocardial infarction is not only ineffective but also harmful. (N Engl J Med 1992;327:227-33.)

LEFT ventricular dysfunction and ventricular premature depolarizations have been shown to predict mortality after myocardial infarction.[1,2] The Cardiac Arrhythmia Suppression Trial (CAST), a multicenter, randomized, placebo-controlled trial, was conducted to test the hypothesis that the suppression of asymptomatic or mildly symptomatic (palpitations without syncope or near-syncope) ventricular premature depolarizations after myocardial infarction would decrease the incidence of death or nonfatal cardiac arrest due to arrhythmias.[3-8] On the basis of a pilot study[6] and a review of other available antiarrhythmic agents, encainide, flecainide, and moricizine were chosen for use in CAST. Patients with an average of at least six ventricular premature depolarizations per hour on base-line ambulatory electrocardiographic recordings and reduced ejection fractions after a myocardial infarction were initially given antiarrhythmic drugs to identify those in whom ventricular ectopic beats could be sufficiently suppressed. If suppression was achieved, the patients were then randomly assigned to receive the effective drug or a matching placebo. Details of the study protocol have been published elsewhere.[7-9]

In April 1989, the Data and Safety Monitoring Board of the CAST study recommended that the encainide and flecainide arms of the study be discontinued because the mortality in these groups was higher than among control patients given placebo. Only 320 patients were being treated with moricizine or its placebo at that time, and an insignificant but favorable trend in mortality was observed among the patients treated with moricizine (11 deaths in the placebo group vs. 4 deaths in the moricizine group). Therefore, the study was continued as CAST-II with moricizine alone. This paper reports the results of the moricizine portion of the study.

METHODS

Six major changes were made to the protocol in CAST-II.[9] First, the study was continued with moricizine, and no new antiarrhythmic drugs were added. Second, the upper limit of eligible values for left ventricular ejection fraction (measured by radionuclide ventriculography in 39 percent of patients, by echocardiography in 29 percent, and by angiography in 32 percent) was lowered from ≤0.55 — the original cutoff point in CAST-I — to ≤0.40. Third, the length of time from the qualifying myocardial infarction to the qualifying ambulatory electrocardiographic recording was shortened from 2 years or less — the interval used in CAST-I — to 90 days or less. Fourth, disqualifying ventricular tachycardia was redefined to exclude from the trial patients with any runs lasting 30 seconds or longer at a rate of ≥120 complexes per minute, but to allow the enrollment of patients with repetitive ventricular complexes of ≥15 beats and lasting up to 30 seconds without symptoms (such patients were excluded from CAST-I). Fifth, a higher dose of moricizine (900 mg per day) was permitted if needed to suppress 80 percent of ventricular premature depolarizations. Finally, because there were no controlled data on the initiation of drug treatment in CAST-I, CAST-II began with a two-week controlled trial of the early effects of low-dose moricizine.

CAST-II thus focused on patients who were more likely to benefit from antiarrhythmic therapy. Recruitment was to continue until January 1, 1992, by which time it was expected that 2200 patients would have been enrolled in the two-week trial and 2100 patients would have been enrolled in the long-term trial. Follow-up was scheduled to continue until April 1, 1994.

In CAST-II, new patients (first screened after April 19, 1989, to determine their eligibility) were considered eligible if an ambulatory electrocardiographic recording obtained 4 to 90 days after an acute myocardial infarction demonstrated at least six ventricular premature depolarizations per hour and if the left ventricular ejection fraction was ≤0.40.

The phase of long-term therapy in CAST-II included 1374 patients whose arrhythmias were suppressed or partially suppressed by moricizine. The patients came from four similar groups: 320 patients had been treated with moricizine or its placebo in CAST-I and simply continued their assigned treatment in CAST-II; 40 patients in whom the dose of antiarrhythmic-drug treatment was being titrated when CAST-I was stopped completed the process of

*For a list of the investigators, see the Appendix.

titration with moricizine and consented to randomization; 216 patients who had been assigned in CAST-I to receive encainide, flecainide, or placebo and whose arrhythmias persisted after the discontinuation of their assigned treatment were subsequently enrolled in CAST-II, given moricizine to determine whether it would suppress the arrhythmias, and randomly assigned to receive moricizine or its placebo; and 798 new patients who met the criteria for CAST-II, and after titration of the drug dose, were randomly assigned to receive moricizine or its placebo.

The short-term trial included 897 patients (887 new patients as well as 10 patients from CAST-I who had been receiving encainide, flecainide, or placebo and who qualified for CAST-II) who were randomly assigned to receive either low-dose moricizine (200 mg every eight hours) or its matching placebo for two weeks. The effects of short-term treatment with moricizine were assessed in an additional 428 patients (enrolled after April 19, 1989, but before the various institutional review boards had approved a change to a placebo-controlled two-week trial) by randomly assigning 211 of the patients to begin immediate assessment receiving moricizine and 217 to receive neither moricizine nor placebo for two weeks. After two weeks, the treatment assignments were unblinded (if placebo-controlled) and patients who had been treated with moricizine were evaluated by ambulatory electrocardiographic recording to determine whether ventricular premature depolarizations were adequately suppressed. Patients who had received placebo or in whom the initiation of therapy was delayed began to have the dose of moricizine titrated and were subsequently evaluated by ambulatory electrocardiographic recording.

Suppression of arrhythmias was deemed adequate if at least 80 percent of ventricular premature depolarizations were suppressed and if at least 90 percent of the runs of nonsustained ventricular tachycardia were suppressed. Titration had to be accomplished within 90 days of the qualifying ambulatory electrocardiographic recording and began with a dose of 200 mg three times daily. If the initial dose did not produce adequate suppression, a second dose (750 mg per day) and, if necessary, a third dose (900 mg per day) were used as long as they were not accompanied by disqualifying adverse effects or symptoms. Patients in whom ventricular premature depolarizations and runs of nonsustained ventricular tachycardia were adequately suppressed were randomly assigned to receive moricizine or its matching placebo in the main study. Patients in whom arrhythmias were only partially suppressed were enrolled in a substudy and randomly assigned to receive moricizine or placebo. Patients in whom arrhythmias either were not suppressed or were increased were not assigned to a study group, although they were still followed.

The primary end point for the short-term, low-dose study was death or cardiac arrest within the two-week period. The primary end point of CAST-II for the main study and the substudy was death due to arrhythmia or cardiac arrest due to arrhythmia requiring resuscitation.[7-10] All events were reviewed by a subcommittee of investigators who were unaware of the treatment-group assignments.

All patients gave informed consent for this study. The research protocol was approved by each center's institutional review board.

Statistical Analysis

Statistical analyses were performed independently for the low-dose, short-term phase and for the long-term treatment phase in order to determine the risk associated with the initiation of therapy and the benefit or risk associated with long-term therapy. Analyses were conducted according to the principle of intention to treat. Though patients given moricizine or its placebo came from the four subgroups outlined above, their data were pooled because the general characteristics of the groups were similar (all had a history of myocardial infarction, ectopic beats, and reduced ejection fractions), and randomization was stratified according to subgroups.

The two-week, low-dose trial was evaluated with a one-tailed test with an α level of 0.05 (during this period, patients were monitored only for the occurrence of harmful effects; evidence of benefit would not in itself have been a reason for stopping the trial). The results of two-tailed tests are also reported. A permutation test based on the randomization assignment (with the chi-square statistic) was employed.[11]

During the long-term phase of the CAST-II study, separate evaluations assessed the effects of moricizine and placebo in patients with adequate suppression of arrhythmias and the effects of moricizine and placebo in patients with only partial suppression of arrhythmias. The long-term study was monitored for both harm (α level, 0.05) and benefit (α level, 0.025). A permutation test based on the randomization assignment (with the log-rank statistic) was employed.[12] The permutation test took into account the various strata imposed by the protocol and by the changes in the protocol from CAST-I to CAST-II.

Both phases of the study used sequential monitoring techniques, and the final P values considered to indicate statistical significance were adjusted accordingly.[13] The conditional power of the tests was also evaluated regularly to assist in monitoring the progress of the study and the advisability of continuing the trial.[14]

An independent Data and Safety Monitoring Board reviewed the data at six-month intervals. They evaluated the potential benefit of and harm from the therapy and the likelihood that the trial would yield meaningful and statistically significant information, based on progress of the study. Decisions were based in part on analyses of conditional power — that is, the chance of observing benefit given the accumulated information.[12-14] At its April 1991 meeting, the board decided, on the basis of the evolving trends in the data, to schedule a meeting in three, rather than six, months. This meeting occurred in July 1991.

RESULTS

The Data and Safety Monitoring Board recommended early termination of CAST-II for two reasons. First, the available data for the two-week, low-dose trial revealed increased mortality among patients treated with moricizine as compared with patients given placebo (15 vs. 3 deaths or cardiac arrests; P<0.021 according to the preliminary classification in July 1991, corresponding to a two-tailed P value of 0.042, adjusted for sequential monitoring, had the trial incorporated a two-tailed design). Second, it appeared very unlikely that the long-term study had any chance of showing improved survival of patients treated with moricizine as compared with those given placebo (42 deaths or cardiac arrests due to arrhythmias during moricizine treatment vs. 32 during placebo, according to the preliminary classification in July 1991).

At the time of the July 1991 meeting of the Data and Safety Monitoring Board, data were still forthcoming. This paper includes the vital status and final classification by the Events Committee of all patients randomly assigned to treatment, except for three patients whose vital status had not been determined as of August 1, 1991 (one receiving moricizine and two receiving placebo) and whose data were censored.

Two-Week, Low-Dose Treatment

During the two-week trial, 1325 patients were randomly assigned to a group — 665 to receive the active drug and 660 to serve as controls. The base-line characteristics of the two groups were similar (Table 1). During this two-week comparison, 17 (2 more than at the initial meeting) of 665 patients who were treated with low-dose moricizine died or had a cardiac arrest (12 during the first week and 5 during the second week), and 3 of 660 patients who were given placebo died (1 during the first week and 2 during the second

Table 1. Base-Line Characteristics of Patients in the Two-Week Evaluation of Treatment and in the Long-Term Study of Moricizine.*

CHARACTERISTIC	TWO-WEEK TREATMENT		LONG-TERM TREATMENT	
	MORICIZINE (N = 665)	PLACEBO (N = 660)	MORICIZINE (N = 691)	PLACEBO (N = 683)
Male sex (%)	82.6	83.5	82.2	83.6
Age (yr)	62.3±9.7	63.0±9.8	61.7±9.9	62.0±10.0
Medical history before MI (%)				
Congestive heart failure	18.9	17.1	15.3	15.5
Angina	48.3	47.1	44.6	44.7
Hypertension	31.9	37.9†	33.6	35.0
Diabetes	21.2	25.6‡	21.5	21.5
Cardiac arrest	3.2	3.3	3.0	2.5
Ventricular tachycardia	3.9	3.6	3.6	3.2
MI	48.0	51.5	47.5	43.3
CABG or PTCA	23.2	21.1	22.3	19.6
Qualifying MI (%)				
Abnormal Q waves	74.7	75.4	77.7	76.1
Old Q waves	25.5	25.7	25.3	25.9
New anterior	25.7	25.5	24.7	23.5
New lateral	8.8	7.8	9.8	7.0
New inferior	20.7	22.7	22.6	20.7
Posterior infarction	8.7	9.0	9.3	9.4
Procedures done since MI (%)				
Thrombolytic therapy	31.1	31.9	31.2	31.1
PTCA	17.4	18.0	16.4	17.2
CABG	17.9	18.5	20.6	19.4
Base-line ambulatory ECG findings				
Heart rate (beats/min)	75.9±15.5	75.8±14.2	76.4±15.5	75.5±15.3
QT interval (sec)	0.38±0.044	0.38±0.041	0.38±0.05	0.38±0.04
Left ventricular hypertrophy	3.8	5.0	3.9	3.4
Mean ejection fraction	31.5±6.9	31.9±7.0	32.3±8.4	32.9±7.9
Ejection fraction ≤0.30	41.0	37.8	42.0	37.7
Final base-line ECG findings				
Ventricular premature depolarizations (no./hr)	124.6±212.4	138.7±238.0	132.5±235.6	141.0±245.8
Fast runs — ≥120 beats/min (no./24 hr)				
0	66.2	67.3	70.2	69.4
1	14.9	15.8	13.7	13.2
≥2	19.0	16.9	16.1	17.4
Concurrent drugs at base line (%)				
Beta-blocker	30.3	27.1	28.1	29.9
Calcium-channel blocker	40.7	40.8	42.5	39.7
Digitalis	31.8	27.4	28.2	26.9
Nitrate	48.5	47.7	41.8	48.0§
Diuretic	44.1	44.4	41.5	41.1
Other antihypertensive agents (including vasodilators)	40.4	42.9	37.5	35.7

*The patients in the short-term study were randomly assigned to receive either moricizine (n = 454) or placebo (n = 443) or to commence treatment with moricizine (n = 211) or delay for two weeks (n = 217). Of the 1374 patients enrolled in the long-term study, 1155 patients had adequate suppression of ectopic beats (581 were then randomly assigned to receive moricizine, and 574 to receive placebo) and 219 had partial suppression of ectopic beats (110 were then randomly assigned to receive moricizine, and 109 to receive placebo). Plus–minus values are means ±SD. MI denotes myocardial infarction, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and ECG electrocardiographic.

†P = 0.02.   ‡P = 0.05.   §P = 0.02.

week), unadjusted P = 0.001; P<0.01 adjusted for sequential monitoring, corresponding to a two-tailed P of 0.002 and less than 0.02 (Fig. 1). The relative risk was 5.6 (95 percent confidence interval, 1.7 to 19.1). Nine patients treated with moricizine died of arrhythmias, five had cardiac arrest due to arrhythmias, and three died of cardiac causes that were not related to arrhythmias. In all three patients in the placebo group who died, death was due to an arrhythmia. In addition to an increased risk of death from all causes, other adverse effects — recurrent myocardial infarction, new or worsened congestive heart failure, and proarrhythmia — also tended to be more common in pa-

tients treated with moricizine in the two-week trial (Table 2).

The Main Study: Long-Term Therapy in Patients with Adequate Suppression of Ectopic Beats

Adequate suppression of ventricular premature depolarizations was achieved in 1155 patients, who were then randomly assigned to receive long-term therapy in the main study — 581 patients to moricizine and 574 patients to placebo. The base-line characteristics of the groups were similar (Table 1), and both groups were followed for a mean of 18 months. More patients in the moricizine group than in the placebo group were not being treated at four months (10.4 percent vs. 6.6 percent) and one year (19.3 percent vs. 12.4 percent). However, the rate of compliance with the medication regimen among patients continuing therapy was identical in the two groups, with 71 percent demonstrating at least 80 percent adherence to the regimen at every pill count.

There were 49 deaths or cardiac arrests due to arrhythmias (7 more than at the time of the initial meeting of the Data and Safety Monitoring Board) among the 581 patients in the moricizine group, as compared with 42 such events (10 more than at the time of the initial meeting) among the 574 patients in the placebo group (two-tailed P = 0.40) (Table 3 and Fig. 2). In the placebo group, 4.8 percent of patients had died of arrhythmias or had a cardiac arrest due to arrhythmias during the first year. Despite these trends, there were no significant differences between groups in the number of deaths or cardiac arrests due to arrhythmias in the long-term phase of the main study. Likewise, there were 87 deaths from any cause or cardiac arrests in the moricizine group and 71 in the placebo group (Table 3), with two-year survival rates of 81.7 percent and 85.6 percent, respectively. The number of deaths or cardiac arrests from cardiac causes other than arrhythmias was similar in the moricizine and placebo groups (23 vs. 20) (Table 3). Nonfatal adverse effects were more common among patients treated with moricizine than among patients given placebo (two-tailed P = 0.03) (Table 2).

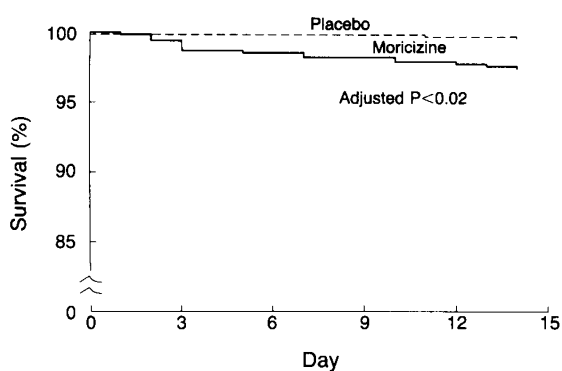In the main study, the likelihood (conditional pow-

er) of observing a significant benefit within the planned duration of the study, given the data available by July 1991, was only 0.078. This estimate was predicated on the mortality at that time, the expected number of additional deaths, an assumed 30 percent reduction in mortality as a result of treatment with moricizine for the balance of the study, and the influence of chance on that 30 percent.

The Substudy: Long-Term Therapy in Patients with Partial Suppression of Ectopic Beats

The substudy of patients with partial suppression of ectopic beats included 219 patients: 110 randomly assigned to receive moricizine and 109 assigned to receive placebo (Table 3). There was a total of 17 deaths in the moricizine group (10 due to arrhythmias) as compared with 15 deaths in the placebo group (9 due to arrhythmias). The similarity of the results and trends in the main study and substudy bolstered the decision of the Data and Safety Monitoring Board to stop the trial.

DISCUSSION

The treatment of patients with asymptomatic or mildly symptomatic ventricular premature depolarizations after a myocardial infarction with the antiarrhythmic drugs evaluated in CAST cannot be recom-

Table 2. Adverse Events among Patients Receiving Moricizine or Placebo during the Two-Week Treatment Evaluation and during Long-Term Therapy.*

ADVERSE EVENT	TWO-WEEK TREATMENT			LONG-TERM TREATMENT		
	MORICIZINE (N = 454)	PLACEBO (N = 443)	P VALUE	MORICIZINE (N = 581)	PLACEBO (N = 574)	P VALUE
	% of patients			% of patients		
Recurrent myocardial infarction	0.7	0.2	—	7.7	7.0	—
New or worsened congestive heart failure	3.7	2.3	—	17.6	13.2	0.04
Proarrhythmia	0.4	0.2	—	0.2	0.2	—
Disqualifying ventricular tachycardia†	0.4	0.2	—	2.1	1.0	—
Other disqualifying ECG findings‡	0	0.2	—	1.4	1.0	—
Severe clinical symptoms§	6.8	2.7	0.004	15.7¶	8.2¶	<0.001

*This analysis includes only the 897 patients randomly assigned to moricizine or placebo in the two-week treatment evaluation and the 1155 patients whose arrhythmias were adequately suppressed and who were randomly assigned to the long-term treatment phase. It excludes 418 patients in the two-week phase who were randomly assigned to begin receiving moricizine immediately or delay treatment for two weeks, and it excludes 219 patients who had only partial suppression of arrhythmias. Some patients had more than one adverse event. ECG denotes electrocardiographic.

†Defined as a heart rate of ≥120 beats per minute lasting for ≥30 seconds.

‡These findings included a QT interval that was at least 1.4 times the base-line value or that was prolonged by at least 0.6 second; a heart rate below 30 beats per minute that lasted at least 1 minute; any pause of at least 3.5 seconds; Mobitz II second-degree heart block; third-degree heart block; and a QRS interval that was at least twice the base-line value or that was prolonged by at least 0.20 second.

§The symptoms were classified as dermatologic, ocular, gastrointestinal, genitourinary, musculoskeletal, neurologic, pulmonary, cardiovascular, or other and excluded the above adverse events. Cumulative adverse events and clinical symptoms were more common among patients treated with moricizine than among those given placebo (two-tailed P = 0.03).

¶Present at four months.

Figure 1. Survival of Patients during the First 14 Days of Treatment with Moricizine or Placebo.

No. at risk (% surviving)
Placebo	660 (100)	659 (99.9)	658 (99.7)
Moricizine	665 (100)	655 (98.5)	608 (97.7)

The end point was death or nonfatal cardiac arrest from any cause. The adjusted P value is based on the log-rank statistic and adjusted for sequential monitoring. Fifty patients who began immediate titration with moricizine completed titration, and their data were censored before 14 days.

mended. CAST-I showed an increased risk of death from treatment with encainide or flecainide. The data from CAST-II demonstrate that the initial two-week exposure to moricizine was also harmful. Because only a low dose of moricizine was given during this two-week period, our findings may be considered to be a minimal estimate of the risk of the initiation of drug therapy if the risk increases as the dose is raised. Whether the risk associated with the initiation of therapy can be avoided by hospitalizing patients, particularly high-risk patients, at the beginning of therapy cannot be answered on the basis of the present CAST-II data, although 12 of the 17 deaths in the moricizine group occurred during the first week of therapy and 10 of the 17 occurred in patients with left ventricular ejection fractions of less than 0.30. Conversely, 5 of the 17 deaths (29 percent) occurred after the first week of therapy, indicating an important ongoing risk, even if hospitalization had been provided for one week. In addition, long-term treatment with moricizine is unlikely to reduce the rates of mortality or major complications. Overall, CAST-I and CAST-II have demonstrated that the suppression of ventricular premature depolarizations by three different drugs not only failed to prevent death from arrhythmias, but also was harmful. No inference can be made from the CAST data with respect to the ability of these drugs to relieve more symptomatic arrhythmias, but the risk of therapy is evident.

Though the relative toxicity of the drugs chosen for CAST as compared with other antiarrhythmic drugs is unknown, the results of CAST-I and CAST-II are consistent with other studies of Class I antiarrhyth-

Table 3. Causes of Death or Cardiac Arrest during Long-Term Blinded Therapy.*

Group	Average Length of Treatment	Arrhythmias		Cardiac Cause Other than Arrhythmia		Noncardiac Cause		Unclassifiable Cause	Total
		Death	RCA	Death	RCA†	Death‡	RCA§		
	days			number of patients					
Main study (suppression of ectopic beats)									
Moricizine (n = 581)	536	42	7 (2)	22	1 (1)	15	0	0	87
Placebo (n = 574)	542	30	12 (6)	18	2 (1)	7	1 (1)	1	71
Substudy (partial suppression of ectopic beats)									
Moricizine (n = 110)	532	10	0	5	0	2	0	0	17
Placebo (n = 109)	589	9	0	5	0	1	0	0	15
Total									
Moricizine (n = 691)	535	52	7 (2)	27	1 (1)	17	0	0	104
Placebo (n = 683)	549	39	12 (6)	23	2 (1)	8	1 (1)	1	86

*RCA denotes resuscitated cardiac arrest. The numbers in parentheses are the numbers of patients who subsequently died.

†In all three patients, cardiac arrest occurred in the setting of class IV heart failure; the patients awoke, but all ultimately died of heart failure.

‡The noncardiac causes of death were cancer (9 patients), pneumonia or respiratory failure (4 patients), stroke or intracranial hemorrhage (4 patients), pulmonary embolus (1 patient), sepsis (2 patients), suicide (2 patients), auto accident (1 patient), hepatic failure (1 patient), and renal failure (1 patient).

§Cardiac arrest in this patient was due to a pulmonary embolus.

mic drugs that report an increased mortality rate in patients after myocardial infarction.[3] A recent meta-analysis has suggested an increased risk of mortality among patients with ventricular arrhythmias treated with quinidine.[15] Studies of mexiletine were inconclusive, but they showed a trend toward worsening mortality.[16] Disopyramide did not improve survival after a myocardial infarction.[17] Analyses of other antiarrhythmic drugs also suggest that they offer no benefit for patients like those treated in CAST.[3] Small studies of amiodarone (a Class III antiarrhythmic agent) after myocardial infarction suggest an improvement in survival.[18,19] We must await the results of larger, placebo-controlled clinical trials with amiodarone in clinical settings similar to those of CAST to determine whether amiodarone is beneficial or harmful.[19] Thus, it is unknown but also unlikely that the use of other Class I antiarrhythmic drugs or even of alternative approaches to treatment with antiarrhythmic drugs will improve survival in patients with asymptomatic or mildly symptomatic ventricular premature depolarizations after a myocardial infarction. Specifically, physicians should not discontinue therapy with antiarrhythmic drugs tested in the CAST study and substitute agents such as quinidine, mexiletine, or other Class I drugs on the assumption that they may be more beneficial in this group of patients.[15,18] Whether antiarrhythmic agents with Class III action are beneficial remains to be proved.

Extrapolation of CAST-I and CAST-II Data to Other Clinical Conditions

It is not known whether treatment with antiarrhythmic drugs is beneficial or harmful in patients with ventricular premature depolarizations associated with other clinical conditions. The extent to which CAST results can be extrapolated to other cardiac conditions, different types of arrhythmias, or drugs not tested in the study cannot be identified with certainty. Antiarrhythmic drugs are frequently used in patients with more serious arrhythmias, including symptomatic nonsustained ventricular tachycardia, sustained ventricular tachycardia, and ventricular fibrillation. In these other patient populations, however, the relative risks and benefits could be different, and therapy is often guided by invasive electrophysiologic testing,[20] whereas some centers use the combination of ambulatory electrocardiographic recording and invasive electrophysiologic testing.[21] In CAST, only patients who had a response to antiarrhythmic drug therapy — that is, suppression of ventricular ectopic beats — were evaluated in the main study. This strategy identified patients at relatively low risk for arrhythmic events.[7,8] It is possible that an apparently drug-induced improvement in the response to therapy, as assessed by electrophysiologic testing, could also simply be an indicator that the patient is at low risk for death from arrhythmias, rather than an indication that the drug has an actual long-term protective effect.[22,23] Whether there is an excess rate of cardiac mortality in any subgroups of these patients with more serious ventricular arrhythmias during treatment with antiarrhythmic drugs is unknown. It is important to recognize that whatever the mechanisms underlying the increased mortality caused by antiarrhythmic drugs in CAST-I and CAST-II, these same mechanisms could also be oper-
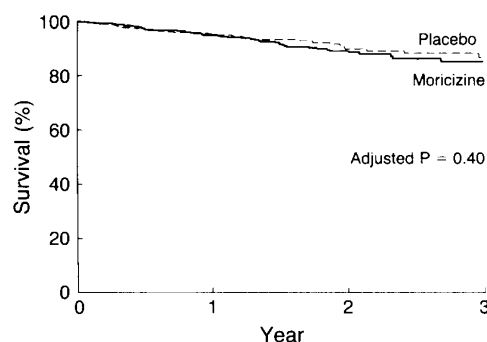
No. at risk (% surviving)
Placebo	574 (100)	351 (95.2)	175 (89.6)	56 (88.0)
Moricizine	581 (100)	350 (94.9)	181 (88.8)	56 (85.0)

Figure 2. Survival of Patients in the Long-Term Main Study during Treatment with Moricizine or Placebo after Adequate Suppression of Ventricular Premature Depolarizations with Moricizine.

The end point was death or nonfatal cardiac arrest due to arrhythmias. The adjusted P value is two-tailed.

ative in other groups of patients. Physicians should use antiarrhythmic drugs with caution in all patient populations. Controlled clinical trials are needed in these other groups of patients to determine the risk of both pharmacologic and nonpharmacologic therapy, as well as the usefulness of electrophysiologic testing.

Clinical Implications

Although the results of CAST-I and CAST-II can be strictly applied only to the use of encainide, flecainide, and moricizine after a myocardial infarction in patients who have asymptomatic or minimally symptomatic ventricular premature depolarizations, the clinical implications may be much broader. The purpose of this study was to evaluate the strategy of detecting and suppressing ventricular premature depolarizations to improve survival after a myocardial infarction. Together, the results of the two studies demonstrate that the hypothesis concerning the suppression of ventricular premature depolarizations is not correct. Suppression of ventricular premature depolarizations after a myocardial infarction by three different Class I antiarrhythmic drugs — encainide, flecainide, and moricizine — actually increased mortality due to arrhythmias. To our knowledge, no study of Class I antiarrhythmic drugs has shown a decrease in mortality in patients after myocardial infarction. Thus, suppression of ventricular arrhythmias has not been linked to improved survival. Furthermore, several studies suggest that treatment of ventricular arrhythmias with antiarrhythmic drugs increases mortality. We conclude that patients with asymptomatic or mildly symptomatic ventricular premature depolarizations after a myocardial infarction should not be treated with antiarrhythmic drugs until improved survival is shown in a controlled clinical trial.

APPENDIX

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