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MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO

The Cardiac Arrhythmia Suppression Trial

DEBRA S. ECHT, M.D., PHILIP R. LIEBSON, M.D., L. BRENT MITCHELL, M.D., ROBERT W. PETERS, M.D., DULCE OBIAS-MANNO, R.N., ALLAN H. BARKER, M.D., DANIEL ARENSBERG, M.D., ANDREA BAKER, R.N., LAWRENCE FRIEDMAN, M.D., H. LEON GREENE, M.D., MELISSA L. HUTHER, DAVID W. RICHARDSON, M.D., AND THE CAST INVESTIGATORS*

Abstract *Background and Methods.* In the Cardiac Arrhythmia Suppression Trial, designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death, patients in whom ventricular ectopy could be suppressed with encainide, flecainide, or moricizine were randomly assigned to receive either active drug or placebo. The use of encainide and flecainide was discontinued because of excess mortality. We examined the mortality and morbidity after randomization to encainide or flecainide or their respective placebo.

Results. Of 1498 patients, 857 were assigned to receive encainide or its placebo (432 to active drug and 425 to placebo) and 641 were assigned to receive flecainide or its placebo (323 to active drug and 318 to placebo). After a mean follow-up of 10 months, 89 patients had died: 59 of arrhythmia (43 receiving drug vs. 16 receiving placebo; P = 0.0004), 22 of nonarrhythmic cardiac causes (17 receiving drug vs. 5 receiving placebo; P = 0.01), and 8 of noncardiac causes (3 receiving drug vs. 5 receiving placebo). Almost all cardiac deaths not due to arrhythmia were attributed to acute myocardial infarction with shock (11 patients receiving drug and 3 receiving placebo) or to chronic congestive heart failure (4 receiving drug and 2 receiving placebo). There were no differences between the patients receiving active drug and those receiving placebo in the incidence of nonlethal disqualifying ventricular tachycardia, proarrhythmia, syncope, need for a permanent pacemaker, congestive heart failure, recurrent myocardial infarction, angina, or need for coronary-artery bypass grafting or angioplasty.

Conclusions. There was an excess of deaths due to arrhythmia and deaths due to shock after acute recurrent myocardial infarction in patients treated with encainide or flecainide. Nonlethal events, however, were equally distributed between the active-drug and placebo groups. The mechanisms underlying the excess mortality during treatment with encainide or flecainide remain unknown. (N Engl J Med 1991; 324:781-8.)

VENTRICULAR premature depolarizations are a risk factor for sudden and nonsudden cardiac death after myocardial infarction[1] and are often treated with antiarrhythmic drugs.[2] Ventricular arrhythmia and left ventricular dysfunction have been found to be independent predictors of cardiac mortality,[3] with more than 10 ventricular premature depolarizations per hour (detected by ambulatory monitoring) associated with a fourfold higher mortality rate.[4] Previous studies have failed to demonstrate that antiarrhythmic therapy reduces the long-term risk of sudden death.[5-15] The Cardiac Arrhythmia Suppression Trial (CAST), a multicenter, randomized, placebo-controlled study, was designed to test whether the suppression of asymptomatic or mildly symptomatic ventricular arrhythmias with antiarrhythmic drug therapy after myocardial infarction would reduce the rate of death due to arrhythmia.

Recruitment for the trial began in June 1987. Three antiarrhythmic agents were studied, on the basis of the results of the Cardiac Arrhythmia Pilot Study (CAPS).[16] That study had shown that encainide, flecainide, and moricizine suppressed arrhythmias adequately in the target population.[17] Recruitment was planned to last three years, from June 1987 to June 1990. However, in April 1989 the Data and Safety Monitoring Board — an independent body responsible for reviewing the results of the trial on a regular basis to protect the patients — recommended that the use of encainide and flecainide be discontinued because the data indicated it was unlikely that benefit could be demonstrated, and it was likely that the drugs were harmful. Encainide and flecainide were discontinued at that time, and a preliminary report of the trial was published.[18] Moricizine is the only antiar-

Supported under contracts with the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Md. Address reprint requests to the CAST Coordinating Center, 1107 NE 45th, Rm. 505, Seattle, WA 98105.

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

rhythmic drug whose use is being continued in the revised CAST (CAST II). This paper details the final analysis of mortality and also reports on morbidity among patients receiving encainide or flecainide or their corresponding placebos.

Methods

The study protocol has been described previously.[18] In brief, patients were eligible for enrollment six days to two years after myocardial infarction if they had an average of six or more ventricular premature depolarizations per hour on ambulatory electrocardiographic monitoring of at least 18 hours' duration, and no runs of ventricular tachycardia of 15 or more beats at a rate of ≥120 beats per minute. Patients were required to have an ejection fraction of 0.55 or less if recruited within 90 days of the myocardial infarction, or 0.40 or less if recruited 90 days or more after the myocardial infarction. Evaluation during an initial, open-label titration period identified patients who responded to one of the drugs with at least 80 percent suppression of ventricular premature depolarizations and at least 90 percent suppression of runs of ventricular tachycardia. Initial open-label drug assignment to encainide, flecainide, or moricizine was in part dependent on the ejection fraction. Flecainide was not given to patients with an ejection fraction below 0.30, to avoid potential aggravation of left ventricular dysfunction.[19,20] Patients with an ejection fraction below 0.30 were randomly assigned to encainide or moricizine as the first or the second drug. Because its ability to suppress ventricular arrhythmias was somewhat less than that of encainide or flecainide, moricizine was used only as a second drug in patients with an ejection fraction of 0.30 or higher.[17] Patients in whom arrhythmias were suppressed were enrolled in the main study and randomly assigned to receive either the effective drug or its corresponding placebo. Patients whose arrhythmias were only partially suppressed were enrolled in a substudy.

The primary end point of the trial was death or cardiac arrest with resuscitation, either of which was due to arrhythmia. Death was defined as the spontaneous cessation of respiration and circulation (pulse) with loss of consciousness, and this end point included cardiac arrest with resuscitation, provided that both cardiopulmonary resuscitation and defibrillation were required.

Death was judged to be due to arrhythmia if it was characterized in any of the following ways: (1) witnessed and instantaneous, without new or accelerating symptoms; (2) witnessed and preceded or accompanied by symptoms attributable to myocardial ischemia in the absence of shock or Class IV congestive heart failure as categorized by the New York Heart Association; (3) witnessed and preceded by symptoms attributable to cardiac arrhythmia — e.g., syncope or near-syncope; or (4) unwitnessed but without evidence of another cause. In the presence of severe congestive heart failure, death was judged to be not due to arrhythmia if death from heart failure appeared probable within four months of the fatal episode.

The principal investigator at the study center was responsible for classifying each death and providing a summary of the circumstances surrounding it, without knowledge of the patient's assigned treatment. The classification and summary were reviewed by a member of the Events Committee. In case of disagreement between the principal investigator and the committee member, the death was classified by the entire committee. All members of the Events Committee were unaware of the patient's assigned treatment. There was agreement between the principal investigator at the center where the death occurred and the primary reviewer of the Events Committee on the classification of 86 percent of deaths.

In addition to the primary end point of death or cardiac arrest due to arrhythmia, the effects of antiarrhythmic drug therapy on other events were also examined. These secondary end points were prospectively defined, as follows: (1) all death or cardiac arrest, defined as death or cardiac arrest (with resuscitation) due to any cause; (2) cardiac death or cardiac arrest, defined as death or cardiac arrest (with resuscitation) due to any cardiac cause; (3) disqualifying ventricular tachycardia (without cardiac arrest), defined as 15 or more consecutive ventricular beats at a rate of ≥120 beats per minute not requiring cardiopulmonary resuscitation and defibrillation for cardioversion, not occurring within 72 hours of an acute myocardial infarction, and not resulting from transient correctable factors such as hypokalemia or an excess of digitalis; (4) syncope, defined as an unexpected, transient loss of consciousness not explained by physical trauma; (5) permanent pacemaker implantation, as judged necessary by the patient's physician; (6) recurrent myocardial infarction, identified according to the same criteria as the qualifying myocardial infarction[18]; (7) congestive heart failure, indicated by the presence of two or more signs or symptoms (dyspnea, easy fatigability, edema, orthopnea, paroxysmal nocturnal dyspnea, jugular venous distention, pulmonary rales, or S_3); congestive heart failure was considered to be new if these findings were not present at base line and was considered to be worsened if the patient's symptomatic state deteriorated by one or more New York Heart Association functional classes; (8) angina pectoris, defined as visceral discomfort with features typical of symptomatic myocardial ischemia; angina was considered to be new if such symptoms were not present at base line and was considered to be worsened if the patient's symptomatic state deteriorated by one or more Canadian Cardiovascular Society functional classes; and (9) coronary-artery revascularization — either coronary-artery bypass grafting or coronary-artery angioplasty — as judged necessary by the patient's physician.

Adverse effects serious enough to require discontinuation of the assigned study medication were similar to the conditions excluding a patient from entry: (1) disqualifying ventricular tachycardia (as defined above as a secondary end point); (2) proarrhythmia, defined as an increase in the frequency of ventricular premature depolarizations by a multiplier that depended on the frequency before treatment,[16] or ≥1500 ventricular premature depolarizations per hour independent of the pretreatment frequency, or as an increase in the frequency of runs of ventricular premature depolarization; in patients with ≥5 runs per day on base-line Holter monitoring, a 10-fold increase was considered to indicate proarrhythmia, and in those with <5 runs per day, ≥50 runs were considered to indicate proarrhythmia; (3) disqualifying electrocardiographic changes: prolongation of the corrected QT interval ≥1.4 times base line or by ≥0.6 second, a heart rate of <30 beats per minute that lasted at least 1 minute, any single pause of ≥3.5 seconds, Mobitz II second-degree, advanced second-degree, or third-degree atrioventicular block, and a QRS interval ≥2 times base line or prolonged by ≥0.20 second; (4) new or worsened congestive heart failure sufficiently serious in the opinion of the attending physician or investigator to require discontinuation of the study medication; (5) a need for treatment with antiarrhythmic agents; and (6) "other adverse" medical events, divided into cardiovascular and noncardiovascular events. Noncardiovascular events included dermatologic, gastrointestinal, genitourinary, neurologic, and psychiatric events or constituted the appearance of multiple symptoms that individually did not meet criteria requiring discontinuation of therapy but that resulted in discontinuation of therapy by the patient or physician.

Compliance with the study medication was assessed by counting the tablets returned by the patient at each visit, and then expressed as a percentage determined from the ratio of the number of tablets missing to the number prescribed. This percentage was calculated for each patient at each visit, and the values for all visits were averaged.

Concomitant drug therapy was assessed at the time of the last clinic visit, according to a standardized checklist for concurrent medication. Medication dosage was not recorded on this form, and no attempt was made to assess compliance with nonstudy medication.

Statistical Analysis

Analysis groups were determined by assignment at randomization, according to the principle of intention to treat. Actuarial curves were calculated with the Kaplan–Meier method.[21] The primary and secondary end points of the active-drug and placebo treatments were compared by standard log-rank tests. Observation began on the day of randomization to blinded therapy and was censored with respect to death or cardiac arrest or with respect to April 18, 1989, the date when the use of encainide and flecainide was discontinued. All reported P values are nominally two-sided, but caution should be used in the interpretation of findings of statis-

tical significance because no adjustment has been made for multiple comparisons. Findings regarding nonfatal adverse events must also be interpreted cautiously, because of the large difference between groups in mortality.

Results

Mortality

We report on completed data collected up to the time of termination of the use of encainide and flecainide (April 18, 1989). Of the 1498 patients assigned to treatment, 89 died or had a cardiac arrest (63 assigned to active drug and 26 assigned to placebo) (Table 1). A significantly greater number of deaths and cardiac arrests due to arrhythmia, cardiac causes, or any cause occurred among patients receiving active drug (encainide or flecainide, whether considered separately or together) than among patients receiving placebo. The relative risk of death or cardiac arrest due to arrhythmia was 2.64 (95 percent confidence interval, 1.60 to 4.36), and that of death or cardiac arrest due to all causes was 2.38 (95 percent confidence interval, 1.59 to 3.57); the actuarial curves are shown in Figures 1 and 2. The relative risk of death or cardiac arrest due to arrhythmia in patients receiving active drug was similar in the subgroup with ejection fractions of less than 0.30 (1.97) and the subgroup with ejection fractions of 0.30 or more (3.38). More cardiac deaths and cardiac arrests not due to arrhythmia also occurred in the active-drug groups than in their corresponding placebo groups. Twenty-two of these deaths (Table 2) were attributed to acute myocardial infarction resulting in cardiogenic shock in 14 patients, to congestive heart failure in 6 patients, and to postoperative coronary-artery bypass grafting in 2 patients. There were eight noncardiac deaths.

Of 81 patients with cardiac death or cardiac arrest, 28 had a witnessed arrest not preceded by symptoms (asymptomatic), 35 had a witnessed symptomatic arrest, and 18 had an unwitnessed arrest. All asymptomatic witnessed arrests, 14 of the 35 witnessed symptomatic arrests, and 17 of the 18 unwitnessed arrests were classified as due to arrhythmia. Of the 42 witnessed deaths or arrests due to arrhythmia, 33 were instantaneous or preceded by symptoms lasting less than 5 minutes, 4 were preceded by symptoms lasting 5 to 60 minutes, and 5 were preceded by symptoms lasting more than 60 minutes. Thus, although the elapsed time from the onset of symptoms to death was not a criterion for death due to arrhythmia, the majority of patients classified as having a witnessed death due to arrhythmia had symptoms for less than one hour. Eight patients classified as having a cardiac death or cardiac arrest had been successfully resuscitated from cardiac arrest (Table 1). Two of the eight cardiac arrests were secondary to congestive heart failure and were not classified as due to arrhythmia.

In 62 of the 89 patients who died the cardiac rhythm was documented electrocardiographically during or after the onset of the lethal event. Thirty-eight of the 59 patients in whom death was attributed to arrhythmia underwent monitoring (60 percent in the active-drug group and 75 percent in the placebo group) (Table 3). In 66 percent of the patients who died of arrhythmia during monitoring, the first arrhythmia detected was ventricular tachycardia or fibrillation. The numbers of patients with ventricular fibrillation detected in the active-drug and placebo groups were the same despite the difference between

Table 1. Cause of Death and Cardiac Arrest (with Resuscitation) in the CAST, According to Treatment Group.

Cause*	Encainide Group		Flecainide Group		Both Groups		Total
	Active drug	Placebo	Active drug	Placebo	Active drug	Placebo	
	number of patients						
Patients in group	432	425	323	318	755	743	1498
All deaths and cardiac arrests	44	19	19	7	63	26†	89
Cardiac death or cardiac arrest	42	15	18	6	60	21‡	81
Arrest with resuscitation	5	1	2	0	7	1	8
Death or arrest due to arrhythmia	29	12	14	4	43	16§	59
Arrest with resuscitation	3	1	2	0	5	1	6
Death or arrest not due to arrhythmia	13	3	4	2	17	5¶	22
Arrest with resuscitation	2	0	0	0	2	0	2
Noncardiac death	2	4	1	1	3	5‖	8

*See Methods for definitions of categories.
†P = 0.0001 for comparison with patients receiving active drug.
‡P<0.0001 for comparison with patients receiving active drug.
§P = 0.0004 for comparison with patients receiving active drug.
¶P = 0.0107 for comparison with patients receiving active drug.
‖P = 0.4822 for comparison with patients receiving active drug.

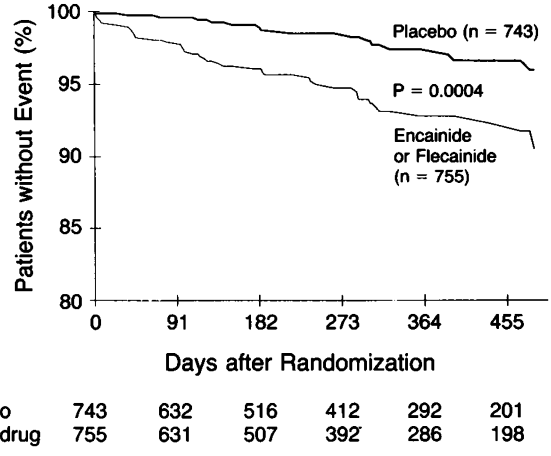
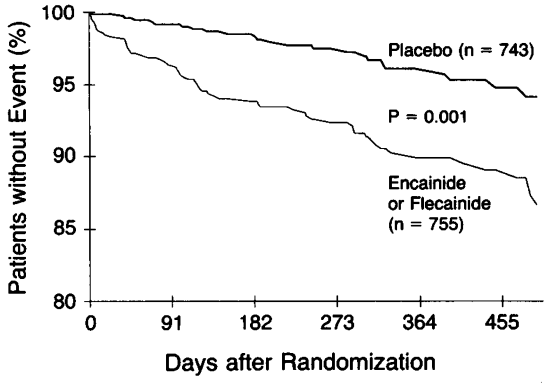


Figure 1. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Arrhythmia in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.
The number of patients at risk of an event is shown along the bottom of the figure.



Placebo	743	625	516	412	292	181
Active drug	755	619	507	392	286	186

Figure 2. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Any Cause in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.
The number at risk is shown along the bottom.

these groups in mortality due to arrhythmia. There was a trend for more of the patients receiving active drug to have ventricular tachycardia or ventricular tachycardia degenerating into ventricular fibrillation on monitoring. More deaths due to arrhythmia in which asystole was the documented rhythm occurred in the active-treatment groups. There were also more patients receiving active drug in whom no monitoring was performed or for whom the monitored rhythm was unknown. Overall, the mean time from the onset of an event to monitoring was similar — 12.4±11.7 minutes in the active-drug groups and 12.1±8.3 minutes in the placebo groups. However, it was notable that the mean time from event to monitoring was shortest when the times in the patients with ventricular tachycardia were combined with those in the patients with ventricular tachycardia degenerating into ventricular fibrillation (6.4 minutes), longer in those with ventricular fibrillation (11.6 minutes), and longest in those with asystole (16.2 minutes). In five patients monitored before and during the event, the rhythm was identified as idioventricular or severe bradycardia; in none of these patients was death attributed to arrhythmia.

Table 2. Causes of Cardiac Death and Cardiac Arrest Not Due to Arrhythmia.

Cause	Encainide Group		Flecainide Group		Both Groups		Total
	Active Drug	Placebo	Active Drug	Placebo	Active Drug	Placebo	
	number of patients						
Myocardial infarction with shock	7	2	4	1	11	3	14
Congestive heart failure	4	1	0	1	4	2	6
Other	2*	0	0	0	2	0	2

*Coronary-artery bypass grafting.

Morbidity

As summarized in Table 4, the incidence of nonlethal cardiac secondary end points was similar in the active-drug and placebo groups, both for each drug alone and for both together. In patients with comparable left ventricular ejection fractions (≥0.30) who were receiving active drug, the incidence of secondary cardiac end points was similar in the encainide and flecainide groups (data not shown).

Adverse Effects

The incidence of adverse effects requiring discontinuation of the study drug (Table 5) was similar in the active-drug and placebo groups. In particular, nonfatal proarrhythmia was not detected in the patients receiving active drug.

Compliance and Concomitant Drug Therapy

During the average 10-month follow-up period, compliance of more than 90 percent was achieved in 70 percent of all patients. The rates of tablet compliance were similar in the active-drug and placebo groups.

Table 3. First Monitored Rhythm in Patients with Death or Arrest Due to Arrhythmia.

Rhythm	Encainide Group		Flecainide Group		Both Groups		Mean Time from Onset to Monitoring
	Active Drug	Placebo	Active Drug	Placebo	Active Drug	Placebo	
	*number of patients**						*minutes*
Ventricular tachycardia	3 (1)	0	0	1	3	1	13.3
Ventricular tachycardia → ventricular fibrillation	2 (2)	1	2 (1)	0	4	1	2.2
Ventricular fibrillation	4 (1)	7	4	1	8	8	11.6
Asystole	7	1	4	1	11	2	16.2
Unknown or not monitored	13	3	4	1	17	4	

*Numbers in parentheses are patients who were monitored before and during event.

Table 6 shows the concomitant drug therapy in each treatment group, as assessed at the last clinic visit for which information was available. There was no significant difference (active drug vs. placebo) in either the encainide or flecainide group in the concomitant use of cardioactive medications. A notable finding was the relatively low incidence of use of beta-blockers (25 to 30 percent) in each treatment group. In contrast, approximately 50 percent of all patients were receiving a calcium-channel–blocking agent. The concomitant drug therapy in the patients with death or cardiac arrest due to arrhythmia differed from the therapy in the other patients, in that fewer of the patients in this subgroup were receiving aspirin and

more were receiving digitalis, diuretics, or nitrates.

Table 4. Nonfatal Cardiac Secondary End Points of the Study.

End Point*	Encainide Group		Flecainide Group		Both Groups	
	Active Drug	Placebo	Active Drug	Placebo	Active Drug	Placebo
	number of patients (number of events per year of exposure)†					
Tachycardia	5 (0.0145)	5 (0.0145)	2 (0.0079)	1 (0.0038)	7 (0.0117)	6 (0.0099)
Syncope	24 (0.0717)	29 (0.0876)	15 (0.0614)	14 (0.0556)	39 (0.0674)	43 (0.0738)
Pacemaker	1 (0.0029)	1 (0.0029)	1 (0.0040)	0 (0)	2 (0.0033)	1 (0.0016)
Infarction	11 (0.0321)	20 (0.0590)	8 (0.0322)	13 (0.0509)	19 (0.0322)	33 (0.0555)
Heart failure	40 (0.1231)	36 (0.1097)	17 (0.0692)	15 (0.0594)	57 (0.0999)	51 (0.0878)
Angina	48 (0.1510)	56 (0.1793)	17 (0.0696)	32 (0.1305)	65 (0.1157)	88 (0.1578)
CABG or PTCA	27 (0.0809)	25 (0.0748)	16 (0.0658)	19 (0.0753)	43 (0.0745)	44 (0.0750)

*Tachycardia denotes ventricular tachycardia without cardiac arrest; pacemaker, implantation of a permanent pacemaker; infarction, recurrent nonfatal myocardial infarction after randomization; heart failure, new or worsened congestive heart failure; angina, new or worsened angina; and CABG or PTCA, coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty.

†In patients who had an event, exposure was defined as the period from the date of randomization to the first occurrence of the event. In patients who did not have that event, exposure was the period from randomization to April 18, 1989, death or cardiac arrest, or withdrawal from the study.

Discussion

Potential Mechanisms Responsible for Mortality

In the CAST study, treatment with encainide or flecainide was associated with a poorer outcome, whether the end point was death due to arrhythmia, death due to any cardiac cause, or death due to any cause. There were no confounding factors identified that could explain the marked difference in mortality rates between the active-drug and placebo groups. Base-line clinical and laboratory characteristics were similar in patients receiving active drug and those receiving placebo. The use of other medications at base line and during follow-up was also similar.

The adverse outcome in patients treated with encainide or flecainide was attributed primarily to unforeseen death or cardiac arrest due to arrhythmia caused by the study drugs. However, it was surprising that there was not a correspondingly higher incidence of nonlethal events involving arrhythmia, such as disqualifying ventricular tachycardia, proarrhythmia, syncope, or need for a permanent pacemaker, in the patients receiving active drug.

The adverse outcome in the patients receiving encainide or flecainide could have reflected proarrhythmic properties of the two agents.[22,23] They slow myocardial conduction velocity profoundly, an effect that might facilitate reentry.[24] These agents do not often suppress the induction of sustained ventricular arrhythmias by programmed stimulation,[25,26] they raise the energy requirement for ventricular defibrillation in experimental models,[27,28] and their use has been associated with an incessant ventricular tachycardia resistant to cardioversion.[29,30] In other studies, potentially lethal ventricular tachycardia developed in 11 percent of encainide-treated patients and 16 percent of flecainide-treated patients.[24] However, the rates of proarrhythmia detected by ambulatory monitoring in both the CAPS and the CAST were extremely low. During drug titration in the CAPS, proarrhythmia developed in 2 percent of patients receiving encainide or flecainide,[5] as compared with 3 percent of patients receiving placebo. In the CAST, after randomization only one patient met the criteria for proarrhythmia, and that patient was receiving placebo. Evidence of proarrhythmia may not have been identified because Holter monitoring was not performed in most patients during follow-up, and exercise testing and electrophysiologic testing were not performed. Incessant ventricular tachycardia was not observed. Although asystole was often the first rhythm recorded in patients at the time of death or cardiac arrest due to arrhythmia, this appeared to be a consequence of the prolonged interval between symptoms and electrocardiographic monitoring rather than of depression of sinus-node function by the drugs. Although it is possible that active metabolites of encainide that are eliminated slowly may accumulate and facilitate proarrhythmic effects,[31] flecainide is not known to form active metabolites. Thus, the lethal events attributed to arrhythmia in the present trial may not fit our preexisting definitions or understanding of proarrhythmia.

Death due to cardiac causes other than arrhythmia was also more common in the patients receiving active drug than in those receiving placebo. The majority of cardiac deaths not due to arrhythmia were attributed to acute myocardial ischemia or recurrent infarction with subsequent cardiogenic shock. There was not a correspondingly higher incidence of angina, nonlethal recurrent acute myocardial infarction, coronary-artery angioplasty, or coronary-artery bypass grafting procedures. However, the total number of deaths and nonlethal ischemic events (angina and nonfatal myo-

Table 5. Adverse Effects Requiring Discontinuation of Study Medication.

Effect*	Encainide Group		Flecainide Group		Both Groups		Total
	Active Drug	Placebo	Active Drug	Placebo	Active Drug	Placebo	
	number of patients						
Disqualifying VT	5	5	2	1	7	6	13
Proarrhythmia	0	0	0	1	0	1	1
Disqualifying ECG	4	1	0	0	4	1	5
Congestive heart failure	7	1	4	4	11	5	16
Other antiarrhythmic treatment	4	2	1	0	5	2	7
Adverse cardiovascular events	2	5	1	3	3	8	11
Adverse noncardiovascular events	7	7	4	6	11	13	24

*VT denotes ventricular tachycardia, and ECG electrocardiogram. See Methods for definitions of disqualifying tachycardia, proarrhythmia, and disqualifying electrocardiogram.

Table 6. Concurrent Use of Nonstudy Drugs at the Time of the Patient's Last Visit.

Drug	Encainide Group		Flecainide Group		Both Groups	
	Active Drug	Placebo	Active Drug	Placebo	Active Drug	Placebo
	number of patients (percent of group)					
Beta-blocker	119	106	85	96	204	202
	(28)	(25)	(26)	(30)	(27)	(27)
Calcium-channel blocker	202	201	171	152	373	353
	(47)	(47)	(53)	(48)	(49)	(48)
Verapamil	11	13	10	8	21	21
	(3)	(3)	(3)	(3)	(3)	(3)
Diltiazem	148	150	124	109	272	259
	(34)	(35)	(38)	(34)	(36)	(35)
Nifedipine	42	36	35	34	77	70
	(10)	(8)	(11)	(11)	(10)	(9)
Digitalis preparation	105	91	57	52	162	143
	(24)	(21)	(18)	(16)	(21)	(19)
Diuretic	170	166	98	89	268	255
	(39)	(39)	(30)	(28)	(35)	(34)
Nitrate	193	178	117	114	310	292
	(45)	(42)	(36)	(36)	(41)	(39)
Other antihypertensive agents	18	16	11	10	29	26
	(4)	(4)	(3)	(3)	(4)	(3)
Aspirin	303	276	218	204	521)	480
	(70)	(65)	(67)	(64)	(69)	(65)
Phenytoin	1	0	3	3	4	3
	(0)		(1)	(1)	(1)	(0)
Individualized therapy*	7	10	2	4	9	14
	(2)	(2)	(1)	(1)	(1)	(2)

*The primary care physician discontinued the study medication and substituted another antiarrhythmic drug.

cardial infarction) was nearly identical in the active-drug and placebo groups. One may speculate that ischemic events occurred equally in these two groups but were more likely to be fatal in the group receiving active drug. Thus, acute myocardial ischemia may have facilitated the occurrence of fatal arrhythmias, or the negative inotropic effects of flecainide and encainide may have resulted in severe hypoperfusion or increased myocardial oxygen demands during acute ischemia. Attributing the excess of deaths to both ischemia and proarrhythmia possibly suggests that these mechanisms are interrelated.

Clinical Implications

The CAST study has demonstrated that the use of encainide or flecainide to treat asymptomatic or mildly symptomatic ventricular arrhythmias in patients with left ventricular dysfunction after myocardial infarction carries a risk of excess mortality. This study emphasizes the need for placebo-controlled clinical trials of antiarrhythmic drugs with end points of related mortality. It also demonstrates the necessity for a data- and safety-monitoring board to establish guidelines for monitoring and discontinuing a study to protect patients.

The lack of benefit of the two Class IC agents used in this study suggests that, despite their increased risk, asymptomatic or mildly symptomatic patients with ventricular premature depolarizations or nonsustained ventricular tachycardia after a myocardial infarction may not benefit from therapy beyond the general use of beta-adrenergic–blocking agents.[32] Although no conclusion can be drawn from the present trial except in regard to the agents and the drug classification studied, it must be noted that trials of other drugs also have not shown a beneficial effect on mortality.[5-15] CAST II will provide information on the efficacy of moricizine in preventing death due to arrhythmia after myocardial infarction.

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Appendix

The investigators of the CAST are as follows: *University of Alabama at Birmingham, Birmingham, Ala.:* William J. Rogers, M.D. (principal investigator), Andrew E. Epstein, M.D., Joaquin G. Arciniegas, M.D., Sharon M. Dailey, M.D., G. Neal Kay, M.D., Randall E. Little, M.D., William A.H. MacLean, M.D., Silvio E. Papapietro, M.D., Vance J. Plumb, M.D., Sigmund Silber, M.D., Andrea R. Baker, R.N., Melanie Cox, Carolynn Thomas, R.N., Donna VonHagel, R.N., and Annie E. Walton, R.N.; *Baylor College of Medicine, Houston:* Craig M. Pratt, M.D. (principal investigator), John Mahmarian, M.D., Terry Eaton, R.N., and Gail Morris, R.N.; *Beth Israel Medical Center, New York:* Thomas Killip, M.D. (principal investigator), Andrew Van Tosh, M.D. (principal investigator), Susan R. Hecht, M.D., George A. Gabor, M.D., Warren A. Kossowsky, M.D., Martin Dolgin, M.D., John E. Madias, M.D., Orest B. Bartoszyk, M.D., Ann Grayeski, R.N., B.S.N., Melissa Flon, R.N., B.S., Ann M. Kelly, R.N., B.S.N., and Mary Louise Conte, R.N., B.S.N.; *Brown University Affiliated Hospitals Center, Providence, R.I.:* Robert J. Capone, M.D. (principal investigator), Lawrence Gorkin, Ph.D., Abdul Hakim Khan, M.D., Kenneth Korr, M.D., Andrew Ross, M.D., Kathy Alberti, R.N., B.S., Emily Connolly, R.N., Pat Rubbert, R.N., B.S., and Tina Cameron, R.N.; *University of Calgary and Cooperating Hospitals, Calgary, Alta.:* D. George Wyse, M.D., Ph.D. (principal investigator), Henry J. Duff, M.D., L. Brent Mitchell, M.D., Anne M. Gillis, M.D., J. Wayne Warnica, M.D., Robert S. Sheldon, M.D., Ph.D., N. Robert Lesoway, M.D., Joyce Kellen, R.N., B.N., Charlotte Hale, R.N., and Karen Hillier, R.N.; *Case Western Reserve University, Cleveland:* Albert L. Waldo, M.D. (principal investigator), Richard W. Henthorn, M.D., Mark D. Carlson, M.D., Joel B. Holland, M.D., Dale Adler, M.D., Robert C. Bahler, M.D., Frank X. Pamelia, M.D., Carol Buchter, M.D., Pammela Redmon, R.N., B.S., Melinda A. Vargas, R.N., B.S.N., and Christopher E. Kobus, R.N., B.S.N.; *Columbia University Affiliated Hospitals, New York:* J. Thomas Bigger, M.D. (principal investigator), Jonathan S. Steinberg, M.D., Judith S. Hochman, M.D., Robert Case, M.D., Henry M. Greenberg, M.D., Edward M. Dwyer, Jr., M.D., John J. Gregory, M.D., Stephen T. Rothbart, M.D., Annmarie Squatrito, R.N., Madeline Kelly, R.N., Jeanne M. Campion, R.N., Deborah Tormey, R.N., Robin Anthony, R.N., Elizabeth Callaghan, R.N., Maureen Chapnick, R.N., Barbara Ripley, L.P.N., R.N., and Cheryl Fontana, R.N.; *Emory University School of Medicine, Atlanta:* Robert C. Schlant, M.D. (principal investigator), Daniel Arensberg, M.D., John D. Cantwell, M.D., J. Arturo Corso, M.D., John W. Hurst, Jr., M.D., Lawrence M. Lesser, M.D., Douglas C. Morris, M.D., Corrine F. Quinn, M.D., Stanley W. Sherman, M.D., Barry D. Silverman, M.D., Mark E. Silverman, M.D., Shirley K. Ballou, M.S., Velma D. Jeffries, R.N., Joy Lee Crowe, R.N., and Janice M. Parrott, R.N.; *George Washington University Medical Center, Washington, D.C.:* Richard J. Katz, M.D. (principal investigator), George A. Besch, M.D., David Brill, M.D., Robert DiBianco, M.D., Dennis Donohue, M.D., Gregory Fisher, M.D., Cleveland Francis, M.D., Dennis Friedman, M.D., Daniel Goldberg, M.D., Samuel Goldberg, M.D., Gregorio Koss, M.D., Louis Larca, M.D., Roger Leonard, M.D., Keith Lindgren, M.D., James Ronan, M.D., Arnold Rosenblatt, M.D., Douglas Rosing, M.D., Allan Ross, M.D., Alberto Rotsztain, M.D., Harry Schwartz, M.D., Fayez Shawl, M.D., Thomas Sinderson, M.D., Roger Stevenson, M.D., Bruce Tinker, M.D., Jacob Varghese, M.D., Mark Weinstein, M.D., John Yackee, M.D., Kay Cross, R.N., Joan Daly, R.N., and Mary Beth Swisher, R.N.; *Gothenburg University, Gothenburg, Swe-*

den: Lars Wilhelmsen, M.D. (principal investigator), Robert Bergstrand, M.D. (principal investigator), Bengt-Olof Fredlund, M.D., Christer Gottfridsson, M.D., Axel Sigurdsson, M.D., Sverker Jern, M.D., Ramon Sivertsson, M.D., Karl Swedberg, M.D., Gunnel Schlyter, R.N., Svisse Haegelind, R.N., Gunnel Hedelin, R.N., and Margareta Leijon, R.N.; *Hahnemann University, Philadelphia:* Joel Morganroth, M.D. (principal investigator), Joseph Carver, M.D., Leonard Horowitz, M.D., Steven Kutalek, M.D., Louis Papa, D.O., James Sandberg, M.D., Mark Victor, M.D., Sharon Cesare, R.N., Brenda Krein, R.N., Chris Vrabel, R.N., Donna Trigone, R.N., Karen Talarico, R.N., Karen Nuschke, R.N., Susan Luhmann, R.N., and Donna Palazzo; *Henry Ford Hospital, Detroit:* Sidney Goldstein, M.D. (principal investigator), A. David Goldberg, M.D., Howard Frumin, M.D., Douglas Westveer, M.D., Michael DeButlier, M.D., John Schairer, D.O., Robert Stomel, D.O., Diane M. Frank, R.N., B.S.N., Regina Jarandilla, R.N., B.S.N., Debbie Davey, R.N., Karen Stemmer, R.N., B.S.N., Chris Thom, R.N., and Elaine Martin, R.N.; *University of Kentucky, Lexington:* Anthony N. DeMaria, M.D. (principal investigator), Chien-Suu Kuo, M.D., James M. Kammerling, M.D., Chris Dunn, R.N., Debra M. Powers, R.N., and Jody Corum, R.N.; *University of Maryland, Baltimore:* Robert Peters, M.D. (principal investigator), Frederick Sutton, M.D., Stephen Gottlieb, M.D., Lisa Martin, M.D., Laurie Todd, R.N., B.S.N., and Cynthia Cusack, R.N., B.S.N.; *University of Massachusetts, Worcester:* Joseph S. Alpert, M.D. (principal investigator), Joel M. Gore, M.D. (principal investigator), S.K. Steven Huang, M.D., Mary Ryan, R.N., and Carol Shustak, R.N.; *University of Minnesota, Minneapolis:* M. Hodges, M.D. (principal investigator), D.M. Salerno, M.D., Ph.D., B. Anderson, M.D., W. Hession, M.D., M. Manoles, M.D., J.M. Haugland, M.D., C. Gornick, M.D., M. Tolins, M.D., D. Berman, M.D., G. Granrud, M.D., J. McBride, M.D., D. Dunbar, M.D., D. Benditt, M.D., S. Riendl, M.D., A. Ettinger, R.N., S. Tait Peterson, R.N., R. Piper, R.N., and R. Slivken, R.N.; *Montreal Heart Institute, Montreal:* Denis Roy, M.D. (principal investigator), Pierre Theroux, M.D., Robert Lemery, M.D., Doris Morissette, R.N., Louise Girard, and Suzanne Ranger; *Oregon Health Sciences University, Portland:* John H. McAnulty, M.D. (principal investigator), Steven E. Reinhart, M.D., Gordon Maurice, M.D., Edward S. Murphy, M.D., Joel E. Cutler, M.D., Jack Kron, M.D., Christy Marchant, R.N., Janie Boxer, R.N., Laurie Princehouse, and the Cardiologists at Southwest Washington Hospitals, Tuality Hospital, Good Samaritan Hospital, Portland Veterans Affairs Hospital, and Providence Medical Center; *University of Ottawa Heart Institute, Ottawa, Ont.:* Donald Beanlands, M.D. (principal investigator), Richard Davies, M.D., Martin Green, M.D., William Williams, M.D., Michael J. Baird, M.D., Linda Warriner, R.N., B.Sc.N., Janet Borthwick, R.N., Liliane Marois, R.N., and Kirsten Woodend, R.N., B.Sc.N.; *University of Rochester, Rochester, N.Y.:* Toshio Akiyama, M.D. (principal investigator), William B. Hood, M.D., Paul N. Yu, M.D., S. Serge Barold, M.D., Robert Easley, Jr., M.D., Richard Kunis, M.D., Gerald Ryan, M.D., John Gillespie, M.D., Laura L. Butler, B.S., Phyllis A. Gehring, R.N., B.S.N., Marcia L. Keller, R.N., B.S.N., Michael Roache, P.A., and Polly Stanley; *Rush–Presbyterian–St. Luke's Medical Center, Chicago:* Pablo Denes, M.D. (principal investigator, 1986 to 1988), James A. Schoenberger, M.D. (principal investigator, 1989 to present), Philip R. Liebson, M.D., Philip E. Hill, M.D., A. Tom Petropoulos, M.D., Joanne Kocourek, R.N., and Cathleen Daly, R.N.; *Salt Lake Clinic Research Foundation, Salt Lake City:* Allan H. Barker, M.D. (principal investigator), Jeffrey L. Anderson, M.D., Robert E. Fowles, M.D., Thomas B. Keith, M.D., C. Basil Williams, M.D., Fidela Moreno, M.D., Ellen N. Doran, Barbara Fowler, Kaye Summers, R.N., and Carla White, L.P.N.; *St. Louis University Medical Center, St. Louis:* Jerome D. Cohen, M.D. (principal investigator), Harold L. Kennedy, M.D., M.P.H., William P. Hamilton, M.D., Thomas A. Buckingham, M.D., Sondra M. Seiler, E.A., and Sally S. Anderson, R.N., B.S.N.; *State University of New York Health Science Center at Brooklyn, Brooklyn:* Nabil El-Sherif, M.D. (principal investigator), Shantha N. Ursell, M.D., Soad Bekheit-Saad, M.D., Arnold M. Einhorn, M.D., Mary Lynn Brezsnyak, R.N., Ann V. Porter, R.N., and Patricia M. Rosa, R.N.; *Vanderbilt University, Nashville:* Raymond L. Woosley, M.D., Ph.D. (principal investigator, 1986 to 1988), Dan M. Roden, M.D. (principal investigator, 1988 to present), W. Barton Campbell, M.D., Debra S. Echt, M.D., John T. Lee, M.D., Judi Diekhoff Spell, R.N., M.S.N., Susan T. Bonhotal, R.N., M.S.N., Leslie L. Jared, R.N., M.S.N., and Tina Ingle Thomas, R.N.; *Medical College of Virginia, Virginia Commonwealth University, Richmond:* David W. Richardson, M.D. (principal investigator), Donald W. Romhilt, M.D. (principal investigator), Kenneth A. Ellenbogen, M.D., Robert A. Bauernfeind, M.D., Barbara B. Bane, Jeanne K. Sanders, R.N., M.S.N., and Sherry F. Shrader, R.N., B.S.N.; *Washington Hospital Center, Washington, D.C.:* Edward V. Platia, M.D. (principal investigator), Susan O'Donoghue, M.D., Cynthia M. Tracy, M.D., Nayab Ali, M.D., Patrick Bowen, M.D., Andrew I. Cohen, M.D., Kenneth M. Brooks, M.D., Andrew J. Keller, M.D., William Oetgen, M.D., Lawrence T. Weston, M.D., Sue Barrett, R.N., Maria R. Johnson, R.N., Diane E. Law, R.N., and Dulce Obias-Manno, R.N.; *Drug Distribution Center, Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M.:* Clair M. Haakenson, R.Ph., M.S., Mike R. Sather, R.Ph., M.S., and Loretta A. Malone; *Coordinating Center, University of Washington, Seattle:* Alfred P. Hallstrom, Ph.D. (principal investigator), Mary Jo Gillespie, M.S., H. Leon Greene, M.D., Yudianto Pawitan, Ph.D., Ruth McBride, Robert Ledingham, M.S., Robin Reynolds-Haertle, M.S., Melissa Huther, and Margit Scholz; *Program Office, Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung and Blood Institute, Bethesda, Md.:* Lawrence M. Friedman, M.D., Eleanor Schron, R.N., M.S., Joel Verter, Ph.D., and Cheryl Jennings; and *Data and Safety Monitoring Board:* Oregon Health Sciences University, Portland — J. David Bristow, M.D. (chairman and principal investigator); University of Wisconsin, Madison — David L. DeMets, Ph.D.; Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis — Charles Fisch, M.D.; University of Colorado Medical School, Denver — Alan S. Nies, M.D.; Harvard Medical School, Boston — Jeremy Ruskin, M.D.; Duke University Medical Center, Durham, N.C. — Harold Strauss, M.D.; and Kennedy Institute of Ethics, Georgetown University, Washington, D.C. — Leroy Walters, Ph.D.

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EFFECT OF A SHORT COURSE OF PREDNISONE IN THE PREVENTION OF EARLY RELAPSE AFTER THE EMERGENCY ROOM TREATMENT OF ACUTE ASTHMA

KENNETH R. CHAPMAN, M.D., P. RICHARD VERBEEK, M.D., JOHN G. WHITE, AND ANTHONY S. REBUCK, M.D.

Abstract *Background.* Relapse after the treatment of acute asthma in the emergency room is common (occurring in 25 to 30 percent of cases) and is not accurately predicted by any available measurements. We studied the usefulness of prednisone in reducing this high rate of relapse.

Methods. One hundred twenty-two patients treated in the emergency room for acute exacerbations of asthma were assigned in a randomized, double-blind fashion to receive at discharge either prednisone for eight days (the dose being tapered from 40 to 0 mg per day) or matching placebo. Ninety-three were subsequently discharged from the emergency room and participated in the trial. On days 1, 7, and 14 after discharge, the patients were assessed during home visits with spirometry and diary-card review; they were contacted by telephone on day 21. Relapse was defined as an unscheduled medical visit occasioned by the patient's perceived need for further asthma treatment.

Results. The overall risk of relapse was significantly lower in the prednisone group ($P<0.05$), with a significantly reduced rate of relapse during the first 10 days of follow-up (3 of 48, as compared with 11 of 45 in the placebo group; $P<0.05$). Thereafter (days 11 though 21), there was no further significant difference in relapse rates between treatment groups (five in the prednisone group and six in the placebo group). During the first week after discharge, patients receiving prednisone reported significantly lower mean ($\pm$SD) daily symptom scores for shortness of breath (1.4 ± 0.4 vs. 2.5 ± 0.4, $P<0.01$) and less frequent use of an inhaled bronchodilator (5.2 ± 0.5 vs. 6.9 ± 0.2 puffs per day, $P<0.05$) than patients receiving placebo. Subsequently, symptom scores and bronchodilator use were similar in the two groups.

Conclusions. A short course of prednisone reduced early relapse rates after the treatment of acute asthma in the emergency room, an effect limited to the period of steroid administration. (N Engl J Med 1991; 324: 788-94.)

PHYSICIANS who treat patients with acute asthmatic attacks can base their therapeutic decisions on numerous studies directed specifically to the care of such patients in the emergency department.[1-3] If hospitalization is required, there is also an extensive body of literature that addresses early in-hospital and intensive care management.[2-4] The decision to admit these patients or discharge them from the emergency room is more problematic. There are no reliable indicators that ensure that patients with asthma who are considered to be well enough to go home from the emergency room will remain well,[3,5-7] and available data indicate that 25 to 30 percent will have a relapse within 10 days of discharge.[8,9] Instructions for follow-up are provided infrequently, and it is unclear what those instructions should be in this critical period.[10] In short, researchers' attention has been focused on the first hour or two of palliation of acute exacerbations of asthma in the emergency room, and less attention has been paid to the subsequent weeks of clinical instability.[2]

How might relapse of recently discharged patients with asthma be prevented? In acute, severe asthma, parenteral corticosteroids administered in a hospital setting can be lifesaving.[11] For the management of stable asthma in ambulatory patients, oral or

From the Asthma Centre of the Toronto Hospital, Toronto. Address reprint requests to Dr. Chapman at the Toronto Hospital Asthma Centre, 399 Bathurst St., 4th Fl., Edith Cavell Wing, Toronto, ON M5T 2S8, Canada.

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