BIOCHEMICAL ANALYSIS PRIZE

Applications for the prize, which is for outstanding and novel work in the field of biochemical analysis or biochemical instrumentation or for significant contributions to the advancement in experimental biology (particularly relating to clinical biochemistry), are now being accepted. Papers, either published or accepted for publication between Oct. 1, 1987, and Sept. 30, 1989, should be submitted before Oct. 15, 1989.

Contact Dr. H. Feldmann, Institute für Physiologische Chemie der Universität, Goethestrasse 33, D-8000 Munich 2, Federal Republic of Germany; or call (49) 89 5-99-61.

POSITRON EMISSION TOMOGRAPHY

The "1st Invitational Conference of the Institute for Clinical PET Practice" will be held in Bermuda, Oct. 26–28.

Contact Inst. for Clinical PET Practice, Suite 700, 1101 Connecticut Ave., NW, Washington, DC 20036; or call (202) 857-1135.

BABY DOE DECISIONMAKING IN THE 1990'S

The conference will be held in Milwaukee, Sept. 14 and 15.

Contact Anne Marie Talsky, Ctr. for the Study of Bioethics, Medical Coll. of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226; or call (414) 257-8498.

REPRODUCTIVE SCIENTIST TRAINING

Applications are being accepted for the program, which is designed to facilitate research training of obstetrician-gynecologists in contemporary research approaches and techniques, and to further progress in the reproductive sciences in medical school departments of obstetrics and gynecology. The program entails a five-year commitment to basic science research. Physicians are encouraged to apply who have completed an approved four-year residency program, who desire to spend several years developing strong basic science skills in addition to their clinical skills, and who are committed to a career in academic obstetrics and gynecology. Deadline for applications is Sept. 15.

Contact Leona Zanetti, Assoc. of Professors of Gynecology and Obstetrics, 409 12th St., SW, Washington, DC 20024; or call (202) 863-2507.

CALL FOR ABSTRACTS

Abstracts are being accepted for a conference, entitled "Temporal Control of Drug Delivery," to take place in New York, Feb. 26–28, 1990. Deadline for submission is Sept. 15, 1989.

Contact Conf. Dept., New York Acad. of Sciences, 2 E. 63rd St., New York, NY 10021; or call (212) 838-0230.

CALL FOR ABSTRACTS

Abstracts are being accepted for the "12th World Congress on Occupational Safety and Health," to be held in Hamburg, Federal Republic of Germany, May 6–11, 1990. Deadline for receipt is October 1, 1989.

Contact Hamburg Messe und Congress GmbH, Postfach 30 24 80, D-2000 Hamburg 36, Federal Republic of Germany; or call (49) 40 35-69-22-42.

SPECIAL REPORT

PRELIMINARY REPORT: EFFECT OF ENCAINIDE AND FLECAINIDE ON MORTALITY IN A RANDOMIZED TRIAL OF ARRHYTHMIA SUPPRESSION AFTER MYOCARDIAL INFARCTION

Abstract The occurrence of ventricular premature depolarizations in survivors of myocardial infarction is a risk factor for subsequent sudden death, but whether antiarrhythmic therapy reduces the risk is not known. The Cardiac Arrhythmia Suppression Trial (CAST) is evaluating the effect of antiarrhythmic therapy (encainide, flecainide, or moricizine) in patients with asymptomatic or mildly symptomatic ventricular arrhythmia (six or more ventricular premature beats per hour) after myocardial infarction.

As of March 30, 1989, 2309 patients had been recruited for the initial drug-titration phase of the study: 1727 (75 percent) had initial suppression of their arrhythmia (as assessed by Holter recording) through the use of one of the three study drugs and had been randomly assigned to receive active drug or placebo. During an average of 10 months of follow-up, the patients treated with active drug had a higher rate of death from arrhythmia than the patients assigned to placebo. Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests (33 of 730 patients taking encainide or flecainide [4.5 percent]; 9 of 725 taking placebo [1.2 percent]; relative risk, 3.6; 95 percent confidence interval, 1.7 to 8.5). They also accounted for the higher total mortality (56 of 730 [7.7 percent] and 22 of 725 [3.0 percent], respectively; relative risk, 2.5; 95 percent confidence interval, 1.6 to 4.5). Because of these results, the part of the trial involving encainide and flecainide has been discontinued.

We conclude that neither encainide nor flecainide should be used in the treatment of patients with asymptomatic or minimally symptomatic ventricular arrhythmia after myocardial infarction, even though these drugs may be effective initially in suppressing ventricular arrhythmia. Whether these results apply to other patients who might be candidates for antiarrhythmic therapy is unknown.

ASYMPTOMATIC ventricular premature depolarizations are a risk factor for sudden death after myocardial infarction,[1,2] and are often treated with antiarrhythmic drugs.[3] 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 after myocardial infarction would reduce the rate of death from arrhythmia. In the Cardiac Arrhythmia Pilot Study,[4] encainide, flecainide, and moricizine were shown to suppress arrhythmias adequately in the target population.[5] Thus, these drugs were selected for use in CAST. CAST begins with an open-label titration period to identify patients who respond to treatment with one of the drugs. The patients who respond are then randomly assigned to receive either the effective therapy or a matching placebo. This design was chosen to test the hypothesis that the suppression of ventricular arrhythmias by antiarrhythmic agents reduces the rate of death from arrhythmia. To avoid aggravation of left ventricular dysfunction, flecainide was not given to patients with an ejection fraction below 0.30.[6,7] Because the ability of moricizine to suppress ventricular arrhythmias was somewhat less than that of encainide or flecainide,[5] moricizine was used as a second drug for patients with an ejection fraction of 0.30 or more. A three-year recruitment was planned, from June 1987 to June 1990, and follow-up is scheduled to end in June 1992.

This paper presents preliminary results of the comparison of encainide and flecainide with their corresponding placebos after an average of 10 months of follow-up.

Methods

Eligibility of Patients

Patients were eligible to be screened for CAST between six days and two years after a documented myocardial infarction. Screening for arrhythmias consisted of an ambulatory electrocardiographic (Holter) recording, with a minimum of 18 hours of analyzable data. The eligibility criterion on the basis of the screening Holter recording was six or more ventricular premature depolarizations per hour.[1] Because the risk of death from arrhythmia after a myocardial infarction decreases with time, and in order to enroll enough potentially high-risk patients to maintain adequate statistical power, a lower ejection fraction was required for patients whose myocardial infarction had occurred more than 90 days before Holter recording.[1,2] If the qualifying Holter recording was obtained within 90 days of the myocardial infarction, a left ventricular ejection fraction of 0.55 or less was required. If the qualifying Holter recording was performed between 90 days and two years after the myocardial infarction, an ejection fraction of 0.40 or less was required. Patients were excluded if they had ventricular arrhythmias causing more severe symptoms (such as syncope or presyncope) resulting from hemodynamic compromise or if they had any unsustained ventricular tachycardia with 15 or more successive beats at a rate of ≥ 120 beats per minute. Palpitations alone did not exclude a patient from participation in CAST. In addition, patients were excluded for reasons of potentially poor compliance, either with therapy or with follow-up; contraindications to any of the drugs being used; other life-threatening conditions; or electrocardiographic abnormalities that would make the interpretation of rhythm difficult. Signed informed consent was required of all patients. The protocol was approved by the institutional review board at each clinical center.

Titration

Patients first underwent an open-label titration phase (averaging 15 days), during which up to three drugs (encainide, flecainide, and moricizine) at two oral doses each were evaluated. The doses of encainide were 35 mg three times daily (dose 1) and 50 mg three times daily (dose 2); of flecainide, 100 mg twice daily (dose 1) and 150 mg twice daily (dose 2); and of moricizine, 200 mg three times daily (dose 1) and 250 mg three times daily (dose 2). The titration was stopped as soon as a drug and dose were found that suppressed the arrhythmias. The criteria for suppression were ≥ 80 percent reduction of ventricular premature depolarizations and ≥ 90 percent reduction of runs of unsustained ventricular tachycardia as measured by 24-hour Holter recording 4 to 10 days after each dose was begun. Patients with a left ventricular ejection fraction of 0.30 or more were randomly assigned to one of two titration sequences: encainide followed by moricizine and then by flecainide or flecainide followed by moricizine and then by encainide. Moricizine was used second in both sequences because it was found to be less efficacious in the suppression of arrhythmias in the pilot study.[4] Patients with an ejection fraction below 0.30 were randomly assigned to receive either encainide followed by moricizine or moricizine followed by encainide. Flecainide was not given to patients with an ejection fraction below 0.30 because of concern about its negative inotropic properties. In our pilot study, encainide and moricizine appeared to be about equally effective in patients with a lower ejection fraction (≤0.30).[5] The titration had to be completed within 90 days of the qualifying Holter recording. Patients whose arrhythmia increased during the open-label titration or who were intolerant of the drugs were not advanced to the randomized phase of the trial. A total of 447 patients (19 percent) fell into this category (or died before randomization). Another 135 patients (6 percent) had only partial suppression of their arrhythmia and did not meet the criteria for effective suppression. These patients were subsequently randomly assigned to receive the "best drug" or placebo, but they are not further described in this article.

Randomization and Follow-up

Patients whose arrhythmias were successfully suppressed were randomly assigned to a treatment group by means of a telephone call to the coordinating center, and had an equal likelihood of receiving the successful drug or a matching placebo. The groups were stratified according to the clinical center, left ventricular ejection fraction (≥0.30 or <0.30), and time between the qualifying Holter recording and the myocardial infarction (≥90 days or <90 days). After randomization, follow-up visits were scheduled at four-month intervals, at which time data were collected on secondary end points such as new or worsened congestive heart failure, sustained ventricular tachycardia, recurrent myocardial infarction, various cardiac procedures, and the quality of life. Compliance with treatment was assessed by counts of study medication.

The primary CAST end point is death from arrhythmia, defined according to criteria developed in the Cardiac Arrhythmia Pilot Study.[8] This definition includes witnessed instantaneous death in the absence of severe congestive heart failure or shock, unwitnessed death with no preceding change in symptoms and for which no other cause can be ascribed, and cardiac arrest. The end point is initially categorized by the local investigator without knowledge of the blinded therapy. Each end point is then reviewed by the Events Committee, a subcommittee of the investigators who are blinded to the treatment each patient received.

Of the deaths included in this report, 78.5 percent had been reviewed and classified by the Events Committee as of the March 30, 1989, analysis date, and the results had 86.3 percent concordance with those of the principal investigator at each clinical center.

Statistical Analysis

CAST was designed as a one-tailed test and was intended to assess whether drug therapy was beneficial or had no beneficial effect, with an alpha level of 0.025 and a power of approximately 0.85. The study was not designed to prove that an antiarrhythmic drug could cause harm. The projected mortality for the primary end point (death from arrhythmia) in the placebo-treated group was 11 percent over an average of three years of follow-up. On the basis of these assumptions and the assumption that the active drug would lead to an estimated 30 percent reduction in the rate of death from arrhythmia, we estimated that the sample size required was 4400 patients.

The Data and Safety Monitoring Board, a group of experts independent of the study investigators, is responsible for evaluating any possible harmful effects of the drugs. The board meets twice yearly to review the unblinded CAST results. It approved an interim monitoring protocol in September 1988, before examining the data. This protocol included a conservative boundary for stopping the study because of demonstrated benefit, a symmetric boundary for advising stopping the study because of adverse effects, and a boundary for stochastic curtailment (i.e., stopping because of a low probability or power of demonstrating a beneficial effect).[9-12] The boundaries were designed to be adaptive to the number of arrhythmic events expected by the planned end of the study. This number was initially estimated to be 425, but the accumulating data as of March 30, 1989, indicated that the total events would probably be less than 300.

For the analyses presented in this paper, base-line comparisons were performed by t-tests and chi-square tests, and primary comparisons were performed by log-rank tests. The significance levels for the individual drug comparisons were increased by a factor of 3 to adjust for multiple comparisons (three independent drug subgroups).[13] Confidence intervals were estimated by the method of Cornfield.[14] The relative risk of treatment in clinically defined subgroups was calculated to evaluate the consistency of the drugs' effects across subgroups.

Results

As of March 30, 1989, a total of 2309 patients had been recruited and were undergoing or had completed

Table 1. Base-Line Characteristics of 1455 Patients Randomly Assigned to Receive Encainide or Flecainide, or Matching Placebo.*

VARIABLE	ENCAINIDE/FLECAINIDE (N = 730)	PLACEBO (N = 725)
Male sex (%)	81.1	83.1
Age (yr)	61±10	61±10
Age (%)		
≤55 yr	26.2	25.8
56–65 yr	38.4	37.0
66–75 yr	30.4	32.3
>75 yr	5.0	4.9
White (%)	82.3	81.7
Ejection fraction	0.40±0.10	0.39±0.09
Ejection fraction (%)		
<0.20	1.9	2.5
0.20–0.29	13.0	12.8
0.30–0.39	33.1	32.3
0.40–0.49	30.9	33.8
0.50–0.55	21.0	18.6
Serum cholesterol (mmol/liter)	5.66±1.33	5.51±1.31
Before MI, history of (%)		
Congestive heart failure	13.7	11.5
Angina	45.9	45.5
Hypertension	30.2	32.8
Diabetes	19.8	20.4
Cardiac arrest	2.2	2.4
VT	2.6	2.2
MI	34.9	37.6
CABG or PTCA	15.9	16.8
Aneurysm/arrhythmia surgery	0.6	0.7
Qualifying MI (%)		
Abnormal Q waves	73.0	74.1
New anterior	20.0	18.2
New lateral	4.8	5.8
New inferior	19.9	18.4
Posterior infarction	9.1	9.9
Abnormal ST elevation	45.0	46.8
Abnormal ST depression	33.9	33.7
Abnormal T inversion	68.3	71.6
Procedures after MI but before randomization (%)		
Thrombolytic therapy	28.2	24.3
PTCA	19.1	18.7
CABG	18.6	18.6
Temporary pacemaker insertion	0.6	1.1
Canadian angina class[15] (%)		
No angina	81.4	80.7
I	8.7	9.1
II	7.7	8.6
III	2.3	1.6
Smoking status (%)		
Current	39.8	39.1
Former	41.4	40.8
Never	18.8	20.1
≥90 Days from MI to Holter recording (%)	21.4	21.9
Base-line electrocardiogram		
PR interval (sec)	0.17±0.03	0.17±0.03
QRS duration (sec)	0.09±0.02	0.09±0.02
QT interval, uncorrected (sec)	0.39±0.04	0.39±0.04
Atrial fibrillation or flutter (%)	2.0	1.3
Left ventricular hypertrophy (%)	4.7	2.7
Paced (%)	0.4	0.3
Base-line Holter recording		
VPD/hr	127±254	128±249
VPD/hr (%)		
≤10	15.1	16.2
10.1–50	39.8	40.7
50.1–100	17.6	15.8
>100	27.5	27.3
VT runs (≥120 beats/min/24 hr) (%)		
None	78.8	79.9
1	10.7	11.4
2–5	6.2	5.2
≥6	4.3	3.5
Atrial fibrillation or flutter (%)	3.5	2.6
Permanent pacemaker (%)	1.1	1.7
LBBB (%)	1.8	1.7
Base-line physical examination		
Sitting heart rate (beats/min)	74±13	73±13
Systolic blood pressure (mm Hg)	126±18	125±18
Diastolic blood pressure (mm Hg)	77±11	76±10
Concurrent drugs at base line (%)		
Beta-blocker	30.4	33.1
Calcium blocker	52.3	49.3
Digitalis	21.2	18.5
Nitrate	47.4	43.7
Diuretic	31.6	31.8
Other antihypertensives	24.2	22.4
Total no. of concurrent drugs (%)		
None	1.1	0.4
1	4.9	4.6
2	17.6	16.4
3	17.3	22.2
4	19.1	20.4
≥5	40.0	36.0

*Plus–minus values are means ±SD. None of the differences were significant. CABG denotes coronary-artery bypass graft surgery, LBBB left bundle-branch block, LVH left ventricular hypertrophy, MI myocardial infarction, PTCA percutaneous transluminal coronary angioplasty, VPD ventricular premature depolarizations, and VT ventricular tachycardia.

the open-label titration phase of the study. Suppression of their arrhythmias had been achieved in 1727 of these patients, and they had been randomly assigned to receive blinded therapy: 1455 had been assigned to encainide, flecainide, or placebo, and 272 to moricizine or placebo.

The CAST Data and Safety Monitoring Board met on April 16 and 17, 1989, reviewed the data that were complete as of March 30, 1989, and recommended that the original study protocol be modified — in particular, that encainide and flecainide be discontinued. This decision was based on the observation that the overall study group (all patients treated with active drug as compared with all patients treated with placebo) had crossed the lower advisory boundary for harm (boundary $Z = -3.11$; observed $Z = -3.22$) and the boundary for stochastic curtailment (boundary power = 0.55; observed power, <0.27).[9-12] In addition, subgroup analysis of each drug and its placebo indicated that the adverse findings for the primary end point were limited to encainide and flecainide, two drugs with Class IC antiarrhythmic action. The results for encainide and flecainide are presented together because the study was not designed to detect individual differences between these two drugs, the results for the two were virtually identical, and both belong to the same class of antiarrhythmic drugs. No significant difference was observed in either direction with respect to moricizine or its placebo. Those results are not reported because the Data and Safety Monitoring Board further recommended that the study be continued with moricizine; therefore, the investigators remain blinded to the effects of moricizine.

The base-line characteristics of the 730 patients randomly assigned to receive flecainide or encainide as compared with the 725 receiving placebo are shown in Table 1. The populations were similar with respect to all characteristics, including age, ejection fraction, time elapsed since myocardial infarction, and use of beta-blockers, calcium-channel blockers, digitalis, or

diuretics at base line. The mean left ventricular ejection fraction was 0.40 in patients treated with encainide or flecainide. Only 2.2 percent of the patients had an ejection fraction below 0.20, whereas 20 percent had an ejection fraction between 0.50 and 0.55. The mean frequency of ventricular premature depolarizations was 127 per hour in drug-treated patients, and 20.6 percent of the patients had at least one run of unsustained ventricular tachycardia (≥120 beats per minute) during their base-line Holter recording. As of March 30, 1989, encainide or flecainide therapy had been withdrawn in 8.4 percent of the patients (4.8 percent for protocol-defined reasons such as major adverse events or symptoms, and 3.6 percent by personal preference or on the advice of their physician), and placebo had been withdrawn in 8.6 percent (3.9 percent and 4.7 percent, respectively). Of the patients still receiving active therapy or placebo, 79 percent were taking at least 80 percent of their medication. Of the patients who died of arrhythmia or were resuscitated after a cardiac arrest, 88 percent were following the study regimen at the time of the event.

Table 2 shows that the number of deaths from arrhythmia, the number of deaths from a nonarrhythmic cardiac event, and total mortality were higher among patients assigned to encainide or flecainide than among those assigned to the corresponding placebo. These data include all deaths reported as of March 30, 1989, and reviewed by the Data and Safety Monitoring Board at its April 1989 meeting. Death from arrhythmia was more common in patients treated with flecainide or encainide (4.5 percent) than in patients given placebo (1.2 percent); the relative risk was 3.6 (95 percent confidence interval, 1.7 to 8.5). The relative risks of death from arrhythmia or cardiac arrest for patients receiving encainide or flecainide considered separately were not different: 3.4 and 4.4, respectively. Survival plots comparing the primary end point of death from arrhythmia among patients receiving placebo and encainide or flecainide are shown in Figure 1. Total mortality was also higher with encainide or flecainide therapy than placebo: 7.7 percent as compared with 3.0 percent (relative risk, 2.5; 95 percent confidence interval, 1.6 to 4.5). The relative risks of mortality from any cause for encainide and flecainide considered separately were not different: 2.7 and 2.2, respectively. The survival plots for total mortality are shown in Figure 2.

Table 2. Events in 1455 Patients Randomly Assigned to Receive Encainide, Flecainide, or Matching Placebo.

Variable	Encainide/ Flecainide (N = 730)	Placebo (N = 725)
Average exposure (day)	293	300
Death from arrhythmia or cardiac arrest	33	9
Other cardiac death	14	6
Noncardiac or unclassified death or cardiac arrest	9	7
Total deaths or cardiac arrests	56	22

Subgroup analyses of base-line covariates revealed a remarkable consistency of drug effect. In all subgroups, patients treated with encainide or flecainide had higher rates of death from all causes and death due to arrhythmia than patients treated with placebo. In particular, the observed increased risk from encainide or flecainide was present regardless of age; use of beta-blockers, calcium-channel blockers, digitalis, or diuretics at base line; or a prolonged QRS interval (Table 3). Patients with an ejection fraction ≥0.30 had an equal chance of being given encainide or flecainide. In this group, the relative risks for encainide and flecainide were virtually identical: 4.6 and 4.4, respectively.

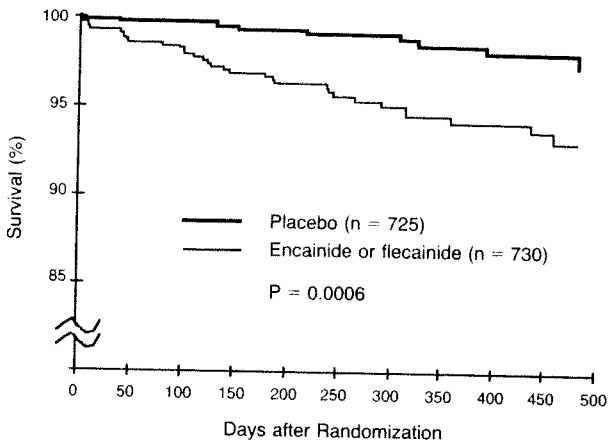

Figure 1. Survival among 1455 Patients Randomly Assigned to Receive Encainide or Flecainide, or Matching Placebo.
The cause of death was arrhythmia or cardiac arrest. The nominal P value was based on a traditional two-sided log-rank test adjusted for multiple groups.

Discussion

After a myocardial infarction, patients have an increased risk of death from arrhythmia and nonarrhythmic cardiac causes. Although many factors contribute to this risk, ventricular premature depolari-

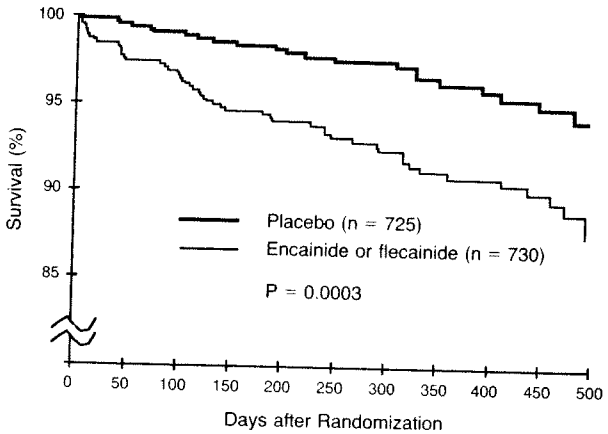

Figure 2. Survival among 1455 Patients Randomly Assigned to Receive Encainide or Flecainide, or Matching Placebo.
The calculations were based on all causes of death. The nominal P value was based on a traditional two-sided log-rank test adjusted for multiple groups.

zations after myocardial infarction confer an independent risk for both death from arrhythmia and deaths from all cardiac causes.[1,2] It has been postulated that the suppression of spontaneous arrhythmias after myocardial infarction would reduce the incidence of sudden arrhythmic death. Previous studies using antiarrhythmic agents to suppress ventricular premature depolarizations have failed to demonstrate improved survival. These studies had too few subjects and often failed to limit enrollment to high-risk patients with arrhythmias.[16-24] CAST was designed to test the hypothesis that the suppression of these asymptomatic or mildly symptomatic arrhythmias would prolong survival.

In this study, drugs are administered until adequate suppression of ventricular premature depolarizations is achieved. Patients are then randomly assigned to receive either that drug or its matching placebo. Therefore, at the time of randomization, the patients have responded to an antiarrhythmic drug. The drugs for the study were chosen because of a documented ability to suppress ventricular premature depolarizations. Encainide and flecainide showed outstanding suppression of ventricular premature depolarizations in the Cardiac Arrhythmia Pilot Study, and moricizine showed good suppression of ventricular arrhythmias and was well tolerated.[5] Other antiarrhythmic agents (such as quinidine, procainamide, disopyramide, mexiletine, and tocainide) were not used because previous studies suggested that they did not suppress arrhythmias as well or that adverse effects precluded their long-term use in a large percentage of patients. Other, newer experimental antiarrhythmic agents were not used because of poor suppression of ventricular premature depolarizations, adverse effects, or lack of enough experience to ensure long-term safety and tolerance by patients.[25]

The rate of death from arrhythmia in the placebo group in CAST was lower than the expected rate. Several possibilities may explain this finding. First, physicians may not have enrolled their sickest patients. Second, the requirement of a response to antiarrhythmic agents may have contributed to the selection of a low-risk population. Third, the deaths during open-label titration (which are not reported in this article) reduced the subsequent death rates in the randomized, placebo-controlled portion of the study. Finally, overall mortality from subsequent events among these patients after myocardial infarction may be lower than that found in previous studies, possibly because of therapeutic developments in recent years (such as thrombolysis). The CAST protocol has been revised to enroll higher-risk patients in the future.

This study was unable to identify any confounding factors to explain the marked difference in mortality rates between the treated and placebo groups. Baseline clinical and laboratory characteristics were similar in those treated with encainide or flecainide and those who received placebo. The results could not be explained by differences in other medications at base line.

Clinical trials are not designed with adequate power to detect the main effect in subgroups or interactions between specific subgroups.[26,27] However, we have chosen to present a series of subgroup results, but only for the purpose of demonstrating the consistency of the estimate of harm. In every subgroup examined, treatment with encainide or flecainide either was harmful or could not be evaluated because of the lack of end points.

Table 3. Primary End Points of the Study: Subgroup Findings.*

Variable	No. of Patients†	Sudden Arrhythmic Death or Cardiac Arrest			Total Deaths or Cardiac Arrests		
		Drug‡	Placebo	Relative Risk	Drug‡	Placebo	Relative Risk
		percent			*percent*		
Treatment assignment, EF ≥0.30							
Encainide or placebo	611	4.6	1.0	4.6	6.8	2.6	2.6
Flecainide or placebo	624	2.9	0.7	4.4	5.1	2.3	2.2
Ejection fraction							
<0.30	220	9.5	3.6	2.7	17.6	6.3	2.8
≥0.30	1235	3.7	0.8	4.5	5.9	2.4	2.4
Digitalis at base line§							
Yes	287	9.8	3.0	3.2	16.2	4.5	3.6
No	1161	3.2	0.9	3.7	5.4	2.7	2.0
Diuretic at base line§							
Yes	459	9.3	2.2	4.2	13.9	5.7	2.5
No	989	2.4	0.8	3.0	4.8	1.8	2.6
Calcium-channel blocker at base line§							
Yes	736	5.0	1.1	4.4	9.4	3.4	2.8
No	712	4.1	1.4	3.0	5.8	2.7	2.1
Beta-blocker at base line§							
Yes	459	4.1	0.8	4.8	6.3	2.5	2.5
No	989	4.8	1.5	3.3	8.3	3.3	2.5
Base-line QRS duration§							
<0.1 sec	896	3.9	1.2	3.4	6.0	2.3	2.6
≥0.1 sec	538	5.8	1.4	4.0	10.4	4.3	2.4
Base-line VPD/hr							
<50	797	2.6	1.5	1.7	5.4	3.2	1.7
≥50	658	6.8	0.9	7.2	10.3	2.8	3.7
MI before qualifying§							
Yes	522	9.6	1.9	5.1	15.0	3.7	4.0
No	918	1.9	0.9	2.1	3.8	2.7	1.4
Time from MI to qualifying Holter recording							
<90 days	1140	4.6	1.6	2.9	7.1	3.4	2.1
≥90 days	315	4.5	0.0	—	9.6	1.9	5.1
Thrombolytic therapy§							
Yes	378	1.5	0.0	—	2.5	0.0	—
No	1062	5.8	1.7	3.5	9.8	4.1	2.4
Age at qualifying Holter recording							
<60 yr	577	3.4	0.7	4.7	5.1	1.8	2.8
≥60 yr	878	5.4	1.6	3.4	9.5	3.8	2.5

*EF denotes ejection fraction, VPD ventricular premature depolarizations, and MI myocardial infarction.

†Approximately half the members in each subgroup received active treatment, and half received placebo.

‡Either encainide or flecainide was given.

§Data missing or incomplete as of the March 30, 1989, cutoff date.

Treatment with encainide or flecainide produced a poorer outcome, whether the end point was death from arrhythmia, death from a nonarrhythmic cardiac cause, death from any cardiac cause, or death from any cause. The classification of death events was quite consistent between the principal investigators at the enrolling centers and the Events Committee, and it was not a determinant of the outcome of the study.

CAST has demonstrated that the use of encainide or flecainide to treat asymptomatic or mildly symptomatic ventricular ectopy in patients with mild-to-moderate left ventricular dysfunction after myocardial infarction causes an excessive mortality risk. Thus, the suppression of ventricular premature depolarizations alone in this population is not an adequate indication that a drug will be helpful in prolonging survival. Encainide and flecainide, two drugs with Class IC antiarrhythmic action[28] that cause marked conduction slowing with less prominent effects on refractoriness, have previously been found to have proarrhythmic effects in patients with structural heart disease and more complex arrhythmias.[28-30] Whether the results of this trial can be extrapolated to other patient groups is unknown. In addition, it appears that each antiarrhythmic drug must be evaluated individually.

This study emphasizes the need for more placebo-controlled clinical trials of antiarrhythmic drugs with mortality end points. It also demonstrates the necessity in such trials of a data- and safety-monitoring board that has established guidelines for monitoring and stopping the study to protect patients.

The CAST Data and Safety Monitoring Board recommended that the study continue with moricizine and possibly with other antiarrhythmic agents that do not have Class IC antiarrhythmic action. Patients with asymptomatic or only mildly symptomatic ventricular premature depolarizations after a myocardial infarction have a twofold to threefold risk of dying as compared with patients without arrhythmia.[1,2] The reduction of this risk, especially among patients with a reduced ejection fraction, is still a highly desirable objective.

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