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Effects of Encainide, Flecainide, Imipramine and Moricizine on Ventricular Arrhythmias During the Year After Acute Myocardial Infarction: The CAPS

THE CARDIAC ARRHYTHMIA PILOT STUDY (CAPS) INVESTIGATORS*

The National Heart, Lung, and Blood Institute initiated the Cardiac Arrhythmia Pilot Study (CAPS) to evaluate the feasibility of suppressing ventricular arrhythmias after acute myocardial infarction. Ten centers enrolled 502 patients younger than 75 years of age with ≥10 ventricular premature complexes (VPC) per hour in a 24-hour electrocardiographic recording and a left ventricular ejection fraction >20%. Patients were enrolled 6 to 60 days after acute myocardial infarction and randomized to 1 of 5 treatment tracks with 2 drugs that included encainide, flecainide, imipramine, moricizine or placebo. During a double-blind drug and dose selection phase, investigators were permitted to change drug or dosage to achieve ≥70% suppression in VPC frequency and >90% suppression of runs of VPC with the exception of patients assigned to placebo, who continued receiving it. Patients were followed for a year after randomization. Patients in the 5 treatment arms were similar in age, sex, clinical characteristics, VPC frequency, left ventricular ejection fraction and concomitant drug treatment. As first drugs, encainide and flecainide had higher efficacy rates, 79% and 83%, respectively, than imipramine, 52%, moricizine, 66%, or placebo, 37%. Encainide and flecainide also had high efficacy rates, 68% and 69%, in patients who failed imipramine or moricizine. Encainide, flecainide and moricizine were well tolerated. These 3 drugs had intolerable adverse effect rates of 6% or less, i.e., similar to placebo. More than 70% of the patients who started the follow-up phase on encainide, flecainide or moricizine remained on these drugs to the end of the study. Imipramine had a high intolerable adverse effect rate. The results of CAPS indicate that large-scale clinical trials to evaluate the effect of ventricular arrhythmia suppression with antiarrhythmic drugs on mortality are feasible.

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Address for reprints: The CAPS Coordinating Center, University of Washington, JD-22, 1107 Northeast 45th, Room 505, Seattle, Washington 98105.

*Members of the Cardiac Arrhythmia Pilot Study (CAPS) are listed in the Appendix.

There is considerable evidence that the presence of ventricular premature complexes (VPCs) predict mortality after acute myocardial infarction (AMI).[1-6] Ruberman[1] showed that complex VPC in a 1-hour electrocardiographic recording identified patients at high risk for both total and sudden cardiac death. Moss et al[2] found that both frequency and complexity of VPC predicted sudden cardiac death and nonsudden cardiac death. Bigger et al[3] showed that ventricular arrhythmias predict mortality independent of left ventricular dysfunction assessed by New York Heart Association class, rales in the coronary care unit and left ventricu-

lar ejection fraction. Similarly, Mukharji et al[4] found that patients with ≥10 VPC/hour had a mortality rate nearly 4 times that of patients with <10 VPC/hour after adjusting for left ventricular ejection fraction.

Given the evidence available, it is reasonable to hope that suppression of ventricular arrhythmias after AMI with antiarrhythmic drugs will improve survival, but there is no significant evidence to support this hypothesis. Furberg[7] summarized the clinical trials in post-AMI patients and emphasized that methodologic problems could account for failure to observe a reduction in mortality with antiarrhythmic therapy. Problems included: (1) inadequate sample size; (2) failure to enroll patients with arrhythmias; (3) failure to assess antiarrhythmic effect; (4) lack of dose titration; and (5) no option to use a second drug if the first failed. Such methodologic problems may have compromised trials with phenytoin, aprindine, mexiletine and tocainide.[8-14]

The National Heart, Lung, and Blood Institute initiated the Cardiac Arrhythmia Pilot Study (CAPS) to obtain knowledge needed for planning a full-scale study to test the hypothesis that long-term suppression of ventricular arrhythmias after AMI with antiarrhythmic drugs will improve survival. Some of the objectives were to: (1) develop methods for identifying and recruiting patients post infarction arrhythmias; (2) develop methods for drug and dose determination in a double-blind clinical trial; (3) determine whether a treatment can suppress VPC rates by at least 70% in about 80% of patients; (4) assess the efficacy and adverse effects of antiarrhythmic drugs over a 1-year period; (5) characterize the natural history of ventricular arrhythmias in the year following AMI; and (6) evaluate the relation between behavioral factors and ventricular arrhythmias after AMI. The present report will provide the results related to the first 4 objectives.

Methods

CAPS was a double-blind, placebo-controlled, randomized trial conducted in 10 clinical centers, a coordinating center, a drug distribution center, a central ambulatory electrocardiogram reading center and the National Heart, Lung, and Blood Institute project office.[15,16] CAPS was divided into 3 phases: (1) patient recruitment; (2) drug and dose selection; and (3) follow-up.

TABLE I Doses of Drugs Used in the Cardiac Arrhythmia Pilot Study

Drug	Total Daily Dose (mg)		
	Low	Medium	High
Encainide	105	150	180
Flecainide	200	300	400
Imipramine	150	225	375
Moricizine	600	750	900

These drugs and a corresponding placebo were donated as follows: encainide by Bristol-Myers Research Laboratories; flecainide by Riker Laboratories; imipramine by Ciba-Geigy; moricizine by DuPont Pharmaceuticals.

Patient recruitment phase: Patients were eligible if they had AMI between 6 and 60 days before enrollment, were <75 years of age and demonstrated either an average of ≥10 VPC/hour or ≥5 episodes of unsustained ventricular tachycardia (3 to 9 consecutive VPCs with a rate of ≥100/min) in a qualifying 24-hour ambulatory electrocardiogram. Patients were excluded if they had a left ventricular ejection fraction ≤20%, contraindications to any of the study medications or ≥10 consecutive VPCs at a rate ≥100/min (disqualifying ventricular tachycardia). Patients with ≥10 consecutive VPCs were excluded because of the concern that their physicians often would want to treat them with conventional antiarrhythmic drugs. If there was inadequate VPC frequency in the first 24-hour ambulatory electrocardiogram, the patient could be screened once more up to 60 days after the AMI.

Drug/dose selection phase: The design of CAPS permitted a comparison of encainide, flecainide, imipramine and moricizine treatment with placebo (Figure 1). After qualifying and giving informed written consent, patients were randomly assigned to 1 of 4 active drugs or to a matching placebo. Three doses of the first drug were permitted (Table I). Dosing continued until efficacy, defined as ≥70% reduction of VPC and >90% reduction in unsustained ventricular tachycardia, was achieved. If efficacy was not achieved or if proarrhythmic effects, disqualifying ventricular tachycardia, conduction abnormalities or other intolerable adverse effects occurred, the patient was switched to a second drug in the treatment arm. Patients who started on a drug with class IC action (i.e., encainide or flecainide) were crossed over to a drug with class IA action (i.e., imipramine or moricizine) and vice versa (Figure 1). Up to 3 doses of the second drug also were permitted. If neither drug in a treatment arm was successful, patients were assigned to the drug that was more efficacious or better tolerated, or both. To detect and manage adverse effects, patients were hospitalized in a monitored setting during the first 48 hours of treatment with the first or second CAPS drug.

Definitions of adverse effects: The CAPS definition of proarrhythmic effect was published previously.[15] It required a 3- to 10-fold increase in VPC frequency and a return to baseline after drug discontinuation. Disqualifying ventricular tachycardia was defined as ≥10 consecutive VPCs at a rate ≥100/min. New or worsening heart failure was defined as hospitalization for heart failure or an increase in diuretic or digitalis dose occurring together with ≥2 signs or symptoms of heart failure, or both. Abnormalities in cardiac impulse formation or conduction were defined as heart rate of ≤30 lasting ≥1 minute, any pause in rhythm ≥3.5 seconds, second-degree Mobitz II atrioventricular block, third-degree atrioventricular block, QRS width ≥0.16 second or a QTc prolongation of ≥50% of the pretreatment control.

Placebo: The placebo comparison group was used to control for variability in VPC frequency during follow-up. Also, the placebo group provided a control for the evaluation of apparent adverse effects of active drugs. The use of placebo was considered ethical be-

cause there is no evidence that suppressing VPC after AMI will reduce the mortality rate. Patients who demonstrated lack of efficacy during treatment with placebo as their first drug were switched to a second placebo (Figure 1).

Follow-up phase: After a drug and dose were selected, patients were followed for 1 year after randomization. Change of study drug or adjustment of dosage was not allowed during the follow-up phase. Patients were evaluated by physical examination and ambulatory 24-hour electrocardiogram at 3, 6, 9 and 12 months. During follow-up, temporary suspension of study medication was allowed for certain surgical procedures and for recurrent myocardial infarction. In the absence of contraindications, the CAPS drug was then restarted. CAPS therapy was discontinued during the follow-up phase because of: (1) disqualifying ventricular tachycardia (≥10 consecutive VPCs); (2) conduction abnormalities; (3) proarrhythmic effect[15]; (4) other intolerable adverse effects; or (5) patient or primary physician decision. Although CAPS was not designed with enough power to assess the potential effect of drug treatment on major clinical events, total and cause-specific mortality and recurrent MI were monitored. After the 12-month evaluation, including a 24-hour continuous electrocardiographic recording, study medication was discontinued. At least 4 days after drug discontinuation, a second 12-month 24-hour electrocardiogram was recorded.

Statistical analysis: The design of CAPS was complex and many comparisons are possible. Because of the selective crossover design, the most valid comparison was by randomization group. However, this comparison obscures differences between drugs. Therefore, the main comparison of efficacy and the assessment of adverse effects of CAPS drugs were made by treatment arm at the end of dose titration on the first drug. Adverse effects during follow-up are presented for actual drug exposure rather than intention to treat because (although the potential for bias exists) it was thought that this was the more conservative and clinically meaningful approach. Comparisons of baseline variables between treatment arms were made by chi-square or analysis of variance, as appropriate. Proportions achieving efficacy or having adverse effects at the end of the drug and dose selection phase were compared by chi-square. Suppression of ventricular arrhythmias during the follow-up phase was evaluated by considering the proportion of patients with an average reduction of VPCs of at least 70% throughout the follow-up year. Percent suppression was computed by dividing the mean hourly VPC rates at the end of dosing, and at 3-, 6-, 9- and 12-month follow-up measures by the mean hourly rates of the baseline and all washout measures (usually the baseline and the 12-month washout). The time to a specific adverse event was analyzed by the method of Kaplan and Meier[17]; comparisons between failure time distributions were made using the log rank statistic.[18]

Results

Clinical characteristics: There were 502 patients enrolled in CAPS. At baseline, there were no overall statistically significant differences among the patients assigned to the 5 treatment arms with respect to age,

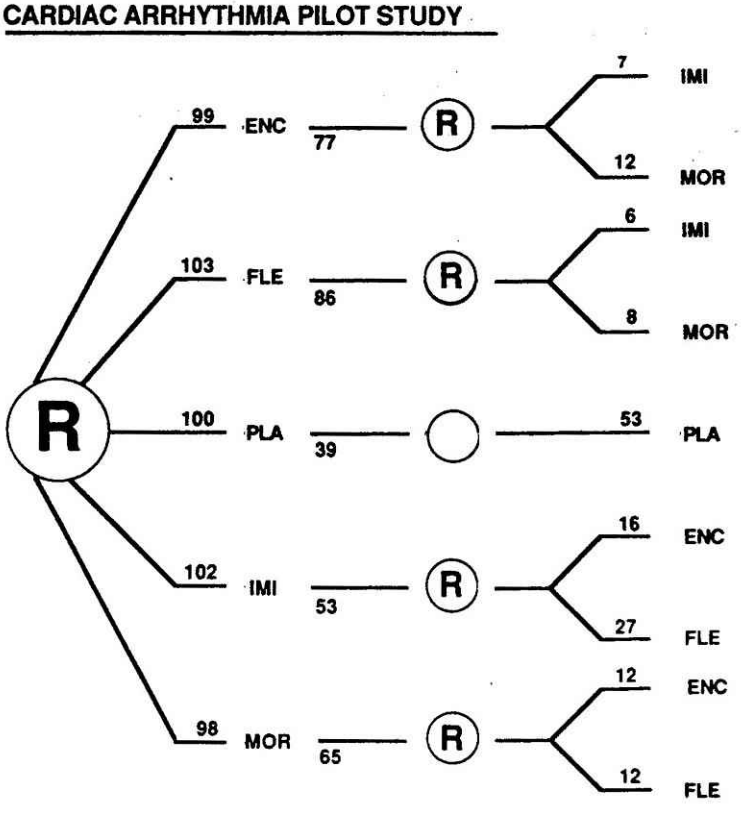

FIGURE 1. Design of the Cardiac Arrhythmia Pilot Study. The *left* column of numbers indicates the number of patients who were randomized to each treatment arm. The *middle* column indicates the number of patients who continued receiving the first drug. The *right* column indicates the number of patients who crossed to a second drug. ENC = encainide; FLE = flecainide; IMI = imipramine; MOR = moricizine; PLA = placebo; R = randomization. For additional information, see Table III.

TABLE II Comparison of Baseline Characteristics by Treatment Arm

Variable	First Drug in Treatment Arm					
	Encainide (n = 99)	Flecainide (n = 103)	Imipramine (n = 102)	Moricizine (n = 98)	Placebo (n = 100)	Total (n = 502)
Age (mean yrs)	59	59	59	59	60	59
Men (%)	85	82	84	85	81	83
Heart failure before AMI (%)	7	4	8	6	6	6
Previous AMI (%)	27	35	26	31	31	30
Family history of angina or AMI (%)	33	35	44	45	28	37
Diabetes mellitus (%)	17	24	9*	13	17	16
Cigarette smoker (%)	35	23	33	35	30	31
VPC/hour (mean)†	138	154	156	144	165	152
<30 (%)	46	36	29	32	30	34
30 to 99 (%)	23	33	32	30	30	30
≥100 (%)	30	31	39	38	40	36
LVEF (mean %)	45	45	46	44	45	45
≥40 (%)	65	63	66	65	67	65
Runs of 3–9 VPC (%)†	38	35	38	28	32	34
Drugs at baseline						
Digitalis (%)	18	25	26	26	20	23
Diuretics (%)	33	35	27	36	30	32
β-blockers (%)	46	36	43	37	41	41
Calcium antagonists (%)	34	51*	42	38	34	40
Potassium supplements (%)	16	16	14	12	18	15

* Statistically significant difference ($p < 0.05$); † dosing baseline Holter.
AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; VPC = ventricular premature complexes.

TABLE III Results During Drug and Dose Selection Phase of CAPS (n = 502)

	Treatment					
	Encainide	Flecainide	Imipramine	Moricizine	Placebo	Total
Randomized	99	103	102	98	100	502
Withdrew before treatment	1	0	0	0	1	2
Started on drug 1	98	103	102	98	99	500
During CAPS drug 1 dosing						
Withdrew	1	2	6	7	5	21
Died	1	1	0	2	2	6
Started CAPS drug 2 dosing	19	14	43	24	53	153
Continued CAPS drug 1	77	86	53	65	39	320
During CAPS drug 2 dosing						
From encainide	—	—	7	12	—	19
From flecainide	—	—	6	8	—	14
From imipramine	16	27	—	—	—	43
From moricizine	12	12	—	—	—	24
Withdrew	4	6	4	5	5	24
Died	0	0	0	1	0	1
Returned to CAPS drug 1	1	0	6	2	7	16
Continued CAPS drug 2	23	33	3	12	41	112
Returned to drug 1 from drug 2	8	0	1	0	7	16
By completion of drug and dose selection						
Assigned to CAPS drug	108	119	57	77	87	448
Withdrew	6	8	10	12	11	47
Died	1	1	0	3	2	7

sex, congestive heart failure, family history of coronary artery disease, smoking, average VPC/hour or ejection fraction (Table II).

Arrhythmia characteristics: All patients had ≥10 VPC/hour in their qualifying Holter recording. In the baseline tape for dosing, an average of 66% of patients (range 53 to 71%) assigned to each treatment arm had ≥30 VPC/hour (Table II); 36% (range 30 to 40%) had 100 VPC/hour or more; and 34% (range 28 to 38%) had 1 or more runs of unsustained ventricular tachycardia (3 to 9 consecutive VPCs).

Results during the drug and dose selection phase: Table III shows the results during the drug and dose selection phase. Two of the 502 patients enrolled withdrew before beginning treatment. During the first step of the drug and dose selection phase, 64% (320 pa-

ients) stayed on the first drug, 4.2% (21 of 500) patients withdrew and 1.2% died (6 of 500). There were 153 patients (31%) in whom CAPS drug 1 lacked efficacy or had intolerable adverse effects. These patients were randomized to CAPS drug 2, with 82% (23 of 28) of them remained on encainide and 85% (33 of 39) flecainide as a second drug, compared to imipramine (23%, 3 of 13) or moricizine (60%, 12 of 20). During dose titration with CAPS drug 2, a total of 112 patients continued receiving drug 2, 16 returned to their first drug, 24 patients withdrew and 1 died. By the completion of the drug and dose selection phase, 89% of the patients (448 of 502) were assigned to a CAPS drug for follow-up: encainide (108), flecainide (119), imipramine (57), moricizine (77) or placebo (87). Patient withdrawal was infrequent during the drug and dose selection phase; only 10.8% of patients either withdrew (9.4%) or died (1.4%).

Time between dose changes: The mean time between dose changes was 11 days during the drug and dose selection phase and was similar for each treatment. The number of days required to complete dosing was shorter for active treatment (encainide 16, flecainide 13, imipramine 20, moricizine 17) than for placebo (32). Patients randomized to placebo required an average of 3.0 dose titration steps compared to 1.7 for active treatment.

Results with CAPS drug 1: Three doses of CAPS drug were permitted and dose titration was continued until efficacy was reached or an adverse effect required switching to another drug in the treatment arm. Table IV describes efficacy and adverse effects of CAPS drug 1 at the completion of dose titration and the reasons for withdrawal during follow-up. Encainide (79%) and flecainide (83%) had higher efficacy rates (>70% VPC and >90% run reduction) than imipramine (52%), moricizine (66%) or placebo (37%) ($p < 0.01$). In addition, encainide, flecainide and moricizine were each more efficacious than placebo ($p < 0.001$). Except for imipramine, efficacy was observed in more patients (76%) with ejection fraction ≥45% than in patients with ejection fraction <45% (64%) ($p < 0.05$). For patients with low left ventricular ejection fraction (<30% or 30 to 44%) moricizine had efficacy rates similar to the drugs with class IC action. At the completion of dose titration on drug 1, there was no significant difference between any of the 5 treatments in the frequency of serious adverse cardiac effects confirmed by drug washout, such as proarrhythmic effect, disqualifying ventricular tachycardia (≥10 consecutive VPCs at a rate of >100/min), conduction abnormalities or heart failure. Imipramine had a 26% incidence of intolerable adverse effects documented by drug washout.

The number of patients who continued receiving the first drug differed: encainide, 85; flecainide, 86; imipramine, 54; moricizine, 65; and placebo, 46. Comparisons of reasons for withdrawal from these groups during follow-up must be viewed cautiously because they no longer contain all of the originally randomized patients. Disqualifying ventricular tachycardia, proarrhythmic effect or syncope that occurred during the follow-up phase, prompted withdrawal from CAPS drug 1 and disappeared during drug washout was seen in 7% of the patients on encainide, 7% on flecainide, 2% on imipramine, 6% on moricizine and 9% on placebo. Death or cardiac arrest occurred during the follow-up phase in 2% of the patients on encainide, 6% on flecainide, 7% on imipramine, 2% on moricizine and 4% on placebo as a first drug. At the end of the study, significantly more patients were taking encainide (64 of 99, 65%) and flecainide (64 of 103, 62%) as first drugs than placebo (35 of 100, 35%).

Results with CAPS drug 2: Findings at the completion of dose titration with CAPS drug 2 were similar to those with CAPS drug 1: encainide (68%) and flecainide (69%) were more effective than imipramine (15%) or moricizine (45%). There were no differences among the CAPS drugs, used as a second drug, in frequency of proarrhythmic effect, disqualifying ventricular tachycardia, conduction abnormalities or heart failure. At the end of the study, the percentage of patients who continued taking CAPS drug 2 were: encainide (20 of 23, 87%); flecainide (25 of 33, 76%); imipramine (2 of 3, 67%) and moricizine (9 of 12, 75%).

Adverse reactions and events in the first 48 hours: Because of concern that serious adverse effects might occur shortly after starting a CAPS drug, patients were hospitalized for at least 48 hours after beginning treatment. There were no differences among treatments with respect to frequency of adverse reactions or events in the first 48 hours (Table V). Serious adverse effects were rare and there were no early deaths that could be ascribed to CAPS treatment. Orthostatic hypotension occurred in 5 patients taking imipramine and was the most frequent early adverse effect.

Adverse effects during the follow-up phase: Reports of moderate to severe adverse effects were analyzed by drug treatment during the follow-up phase

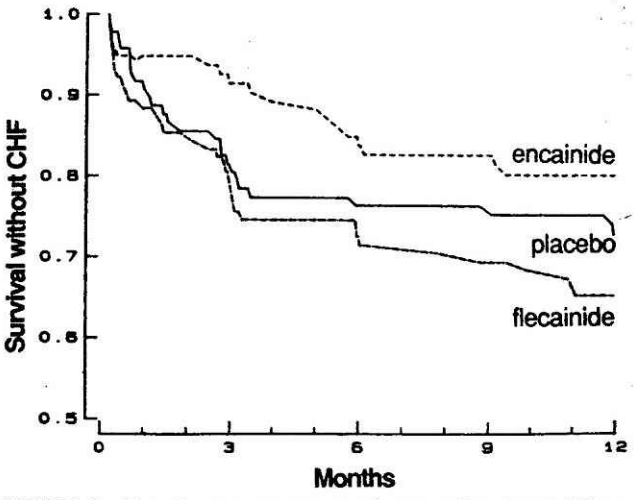

FIGURE 2. Time to new or worsened congestive heart failure (Kaplan-Meier method). Patients randomized to the placebo group, the encainide-imipramine/moricizine treatment arm, or the flecainide-imipramine/moricizine treatment arm are compared. Patients were censored when death or cardiac arrest occurred.

TABLE IV Results of Treatment with First Drug in the CAPS Treatment Arms

	Drug				
	Encainide (n = 99)	Flecainide (n = 103)	Imipramine (n = 102)	Moricizine (n = 98)	Placebo (n = 100)
During the Drug and Dose Selection Phase					
Effective (%)	79	83	52	66	37
LVEF <30%	67	64	47	55	22
LVEF 30–44%	69	79	59	64	36
LVEF ≥45%	90	91	49	73	41
Not effective* (%)	10	3	16	15	41
Adverse effects confirmed by drug washout					
Proarrhythmic (%)	1	3	1	1	3
Disqualifying VT (%)	1	2	2	2	6
Conduction abnormalities (%)	3	3	3	3	0
Heart failure (%)	0	2	1	0	0
Other intolerable adverse effects (%)	5	5	26	6	3
Not confirmed by drug washout					
Heart failure (%)	0	1	0	0	1
Death, cardiac arrest or VT (%)	1	1	0	4	2
Did not complete dosing and no probable cause ascribable (%)	2	0	2	4	7
During the Follow-Up Phase					
No. on drug 1 at end of dosing	85	86	54	65	46
No. on drug 1 at end of study	64	64	34	48	35
Reasons for withdrawal from drug 1					
Death or cardiac arrest (%)	2	6	7	2	4
VT, proarrhythmia or syncope (%)	7	7	2	6	9
Heart failure (%)	1	3	2	2	0
Recurrent infarction (%)	1	0	0	2	0
Other adverse effects (%)	7	6	17	9	4
Miscellaneous (%)	6	3	9	6	7

* Not effective without any serious adverse effect.
LVEF = left ventricular ejection fraction; VT = ventricular tachycardia (10 or more consecutive ventricular premature depolarizations).

TABLE V First CAPS Drug: Number of Adverse Reactions and Events in the First 48 Hours

	Drug					
Adverse Reaction or Event	Encainide (n = 99)	Flecainide (n = 103)	Imipramine (n = 102)	Moricizine (n = 98)	Placebo (n = 100)	Total (n = 502)
Death	0	0	0	0	0	0
Disqualifying ventricular tachycardia	1	0	2	1	1	5
Conduction abnormalities	0	0	0	1	2	3
Congestive heart failure	1	0	0	1	0	2
Recurrent myocardial infarction	0	0	0	1	2	3
Orthostatic hypotension	0	1	5	0	0	6
Other serious adverse effects	0	1	1	0	0	2
Total	2	2	8	4	5	21

(Table VI). The incidence of any adverse effect was lower for encainide (49%) and flecainide (55%) than for imipramine (67%), moricizine (64%) or placebo (60%). The most common *cardiovascular adverse effect* was dizziness upon standing for moricizine and imipramine (approximately 10%); *gastrointestinal adverse effects* (dry mouth, constipation) were seen most often after imipramine (44%); *genitourinary adverse effects* (decrease in sexual activity, difficulty urinating) occurred most often after encainide, flecainide and moricizine (15 to 18%); *neurologic adverse effects* (poor coordination, clumsiness or stumbling, dizziness or lightheadedness, numbness or tingling) were common for all treatments, including placebo (38%). Imipramine was the only treatment discontinued more frequently (18%) than placebo (7%) because of adverse symptoms (Table VI).

Heart failure: The actuarial 1-year incidence of heart failure was high in CAPS (25%). There was no statistically significant difference between all active treatments and placebo in the incidence of heart failure. In addition, there were no differences between the groups receiving encainide (20%) or flecainide (35%) and the placebo group (27%) (Figure 2).

Compliance: Compliance during the drug and dose selection phase was excellent for each treatment: 90%

TABLE VI Moderate to Severe Adverse Effects Reported Between the End of Drug and Dose Selection Phase and End of Follow-Up Phase (%)*

Category	Drug Assigned at End of Dosing				
	Encainide (n = 108)	Flecainide (n = 119)	Imipramine (n = 57)	Moricizine (n = 77)	Placebo (n = 87)
Cardiovascular	17	19	25	23	21
Dizziness on standing	5	5	9	10	0
Fast/irregular heart beat	6	5	2	10	8
Syncope or near syncope	2	3	5	1	2
Wheezing	6	6	2	8	5
Cutaneous†	3	3	4	6	3
Gastrointestinal‡	13	19	44	26	21
Genitourinary§	16	15	11	18	11
Neurologic‖	22	29	30	34	38
Other¶	31	32	37	44	43
Any symptom	49	55	67	64	60
Stopped drug because of symptom	2	3	18	6	7

* Only adverse effects reported while taking the drug assigned at the end of the drug and dose selection phase were counted; † burning or prickling of the skin; skin rash; ‡ dry mouth; nausea; vomiting; abdominal pain; diarrhea; constipation; § difficulty urinating; decrease in sexual activity; ‖ poor coordination; dizziness or lightheadedness; numbness or tingling; blurred vision; drowsiness; stuttering; tremor; nightmares; insomnia; ¶ headache; abnormal sense of well being; seeing or hearing things that aren't real; restlessness or nervousness; frequent depression that interferes with work, recreation or sleep; unusual tiredness or fatigue; fever.

had at least 80% compliance at each pill count (range 86 to 96%). During the follow-up phase, at least 80% compliance was noted in 71% taking encainide and 80% taking flecainide.

Mortality: There were no significant differences in mortality rate among the treatments. It was recognized during the design of CAPS that the number of fatal or major arrhythmic events would be insufficient to detect a treatment effect.

Discussion

Ventricular arrhythmias have been identified as an independent risk factor for cardiac mortality following AMI. To test the hypothesis that VPC suppression after AMI improves survival, adequate numbers of patients with significant ventricular arrhythmias will have to be enrolled, randomized to effective and tolerated antiarrhythmic agents or placebo and followed. To date, no large-scale clinical trials to test this hypothesis have been performed.[7] CAPS was undertaken to determine whether it is feasible to carry out such a study. The goals of CAPS were achieved, paving the way for a subsequent large-scale trial to assess effects of VPC suppression on mortality.

Feasibility: The CAPS showed that: (1) it is possible to identify and recruit suitable subjects for a definitive trial; (2) well tolerated, highly efficacious antiarrhythmic agents exist for ventricular arrhythmias after AMI; (3) dose titration with multiple drugs is feasible under clinical trial conditions; and (4) patient compliance and follow-up can be maintained in a postinfarction cohort. CAPS also showed that large numbers of patients must be screened to identify and enroll a sufficient number of qualified postinfarction patients.[16] Nearly 4,000 patients met other eligibility criteria and were screened with a 24-hour electrocardiographic recording to enroll 502 eligible patients. Additionally, CAPS showed that 2 drugs, encainide and flecainide, successfully suppress VPC after AMI, with no more adverse effects than placebo and with excellent compliance. Efficacy rates would have been lower and withdrawal rates higher had CAPS used only 1 dose level of 1 drug.

Drug efficacy and overall adverse effects with placebo: The placebo treatment arm permitted us to observe the natural history of ventricular arrhythmias after AMI. The apparent efficacy of 37% during dose titration with placebo reflected the high degree of spontaneous variability in VPC frequency and more frequent recording in the placebo group. The high frequency of apparent efficacy in this group must be considered in the design and analysis of any large-scale mortality reduction trial. The adverse effects encountered in the placebo treatment arm were compared with the active treatment arms. During treatment with a first drug (Table IV), there was no significant difference between placebo and active drugs in the incidence of conduction abnormalities, congestive heart failure or proarrhythmic effects. Similarly, in both the drug and dose selection and follow-up phases (Tables IV and VI), there was no difference between placebo, encainide, flecainide and moricizine in the incidence of intolerable noncardiac adverse effects.

Drug efficacy and overall adverse effects with active drugs: CAPS drugs with class IC action were more effective in suppressing ventricular arrhythmias than drugs with IA action. In both the drug and dose selection and follow-up phases, the efficacy of encainide and of flecainide was similar and superior to imipramine and moricizine (Table IV). However, the efficacy of moricizine approached that of encainide and flecainide when it was used as the first drug in patients with low left ventricular ejection fraction (<30 or <45%) or

as the second drug. Twelve of 20 patients who took moricizine as a second drug were assigned to it at the start of the follow-up phase (Table III).

The superior efficacy of encainide and flecainide was not associated with a higher frequency of adverse effects. Encainide and flecainide were similar to each other in their adverse effect profile and tended to have fewer adverse effects than imipramine, moricizine or placebo (Tables IV to VI). No drug was different from placebo with respect to heart failure, but flecainide had a slightly higher incidence of moderate to severe heart failure than encainide (Figure 2). Considering the multiple comparisons, the latter difference was not statistically significant. Whether this finding has clinical significance is uncertain. Previous studies have shown that flecainide can aggravate heart failure, particularly in patients in New York Heart Association functional classes III and IV and left ventricular ejection fraction <30%.[19] Overall, fewer than 5% of the patients had to stop the CAPS drug because of heart failure during drug and dose selection or follow-up phases. Other adverse effects tended to occur less frequently on drugs with class IC action than on drugs with class IA action. Thus, encainide and flecainide are not only effective for treating ventricular arrhythmias after AMI but also are safe and well tolerated.

Additional comments: Because of the exclusion criteria used in CAPS, one cannot extrapolate the results to the entire post-AMI population. CAPS excluded patients with ventricular tachycardia ≥10 complexes and left ventricular ejection fraction ≤20%. Aggravation of heart failure or proarrhythmia might occur more frequently in patients with left ventricular ejection fraction ≤20% or sustained ventricular tachycardia, were they exposed to these drugs.[19,20]

CAPS was the first trial to compare encainide and flecainide after AMI. These drugs had high efficacy rates and were well tolerated in the year after infarction. This finding is consistent with previous studies in other populations.[21-24] Currently, the use of antiarrhythmic drugs after AMI in asymptomatic patients is of unproven value. The Cardiac Arrhythmia Suppression Trial is assessing the ability of long-term suppression of ventricular arrhythmias after AMI to reduce the sudden cardiac death rate.

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Appendix—The Cardiac Arrhythmia Pilot Study Investigators

University of Alabama at Birmingham: Albert L. Waldo, MD*, William J. Rogers, MD*, Richard W. Henthorn, MD, Brian Olshansky, MD, Andrew E. Epstein, MD, Albert Oberman, MD, Mark D. Cohen, MD, Paul Hess, MD, Coordinators: Donna Kerns, RN, Terry Glickman, RN.

Baylor College of Medicine: Craig M. Pratt, MD*, J. Alan Herd, MD, Christopher R. Wyndham, MD, Allen Seals, MD, Miguel Quinones, MD, Robert Roberts, MD, Mario Verani, MD, James Young, MD, Coordinators: Amy Galloway, RN, Ann Riordan, RN, Pat Carlson, RN, Beth C. Thornton, RN.

Brown University Affiliated Hospitals: Robert J. Capone, MD*, Edward W. Bough, MD, David Ahern, PhD, Michael Follick, PhD, Larry Gorkin, PhD, Abdul H. Khan, MD, Suh-Dong Hahn, MD, Henry Gerwitz, MD, Gregory Macina, MD, Gary Heller, MD, Richard Carleton, MD, Coordinators: Kathryn Alberti, RN,