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Classification by Type of Ventricular Arrhythmia Predicts Frequency of Adverse Cardiac Events From Flecainide

JOEL MORGANROTH, MD, FACC,* JEFFREY L. ANDERSON, MD, FACC,†
GARY D. GENTZKOW, MD‡

Philadelphia, Pennsylvania, Salt Lake City, Utah and St. Paul, Minnesota

Antiarrhythmic therapy is known to be associated with a significant risk of adverse cardiac reactions, including a proarrhythmic response. This study assessed in 1,330 patients followed up for 292 ± 393 days the predictive value for cardiovascular safety of a system by which patients were classified according to ventricular arrhythmias on entry, presence or absence of organic heart disease and drug dose for flecainide acetate. Baseline arrhythmia subgroups included patients with 1) premature ventricular complexes only, 2) nonsustained ventricular tachycardia, and 3) sustained ventricular tachycardia.

Proarrhythmic events occurred in 6.8% of patients overall and were serious in 2.3% and lethal in 1.0%. However, proarrhythmia was highly dependent on arrhythmia class on entry: serious nonlethal proarrhythmic events occurred in 6.6% of patients with sustained ventricular tachycardia, only 0.9% with nonsustained ventricular tachycardia and 0% with premature ventricular complexes ($p < 0.01$). Proarrhythmic death occurred in 3.1% of patients with sustained ventricular tachycardia, 0.2% with nonsustained ventricular tachycardia and 0% with premature ventricular complexes only ($p < 0.01$). Proarrhythmia was also influenced by the presence of structural heart disease: serious nonlethal proarrhythmia occurred in 2.6% of patients with versus 0.4% of those without organic heart disease, and death occurred in 1.2 versus 0%, respectively. These adverse events were also dependent on dosing regimen. Flecainide caused premature discontinuation due to new or worsened heart failure in 1.4% of patients, all with underlying organic heart disease; however, heart failure was not clearly related to dose or type of arrhythmia. Symptomatic conduction disturbances occurred in 2.2%, and were predicted by preexistent sinus node disease but not by other baseline features.

The safety of flecainide was markedly enhanced by a slow, incremental approach to dosing, especially in high risk patients. Because most proarrhythmia occurred early during dose finding, hospitalization for drug initiation would appear to improve safety in patients with sustained ventricular tachycardia, heart failure and sinus node dysfunction. These data confirm the usefulness of a clinical classification system based on severity of rhythm disorder and presence of structural heart disease in predicting serious adverse proarrhythmic events with flecainide.

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Over the past few years, intense study of new antiarrhythmic agents has shown that this class of drugs has the potential for life-threatening side effects (1). A reassessment of the risk/benefit ratio of using antiarrhythmic agents is thus necessary. The physician now must not only consider the electrocardiographic diagnosis of the ventricular arrhythmia type in assessing this risk/benefit relation, but also must determine whether the arrhythmia is likely to be benign, potentially lethal or lethal to the patient (2). Criteria for such a classification based on clinical experience have been suggested, including consideration of the degree of structural heart disease and the hemodynamic consequences of the ventricular arrhythmia. New potent antiarrhythmic agents that belong to the modified Vaughn-Williams classification IC have recently been made available (3). Such agents need to be assessed to determine their potential to cause proarrhythmic or other adverse cardiac events.

The objective of this study was to evaluate the incidence of life-threatening or serious adverse cardiac reactions to the use of the newly available class IC antiarrhythmic agent flecainide in patients at various degrees of risk: those with or without structural heart disease, those with arrhythmias

From the *Likoff Cardiovascular Institute, Hahnemann University Hospital, Philadelphia, Pennsylvania; †University of Utah School of Medicine and the Latter Day Saints Hospital, Salt Lake City, Utah; and ‡Riker Laboratories, Inc., 3M Company, St. Paul, Minnesota.

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Address for reprints: Joel Morganroth, MD, Likoff Cardiovascular Institute, Hahnemann University Hospital, Broad and Vine Streets, Philadelphia, Pennsylvania 19102.

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of different levels of seventy and those treated with high versus lower initial doses. Such an evaluation may serve as the basis for developing a clinical approach to the use of flecainide that will optimize its benefit and minimize its risk.

Methods

The flecainide data base. The flecainide clinical efficacy and safety data base (St. Paul, Minnesota) collected from February 1980 to July 1985 was reviewed retrospectively to define the relative risks of death and serious adverse cardiac experiences in a patient population stratified for severity of underlying ventricular arrhythmia, presence or absence of structural heart disease, dose of flecainide administered and administration of flecainide as part of outpatient or inpatient therapy. This data base comprised 1,330 patients derived from the United States data base plus two European trials, as follows:

1. An early in-hospital dose-ranging study and its long-term follow-up in 37 patients (4–6).
2. An outpatient double-blind parallel-designed comparative study of flecainide versus quinidine and its long-term follow-up in 260 patients (7).
3. A prematurely discontinued attempt at studying flecainide in 10 patients in the early postmyocardial infarction period.
4. A study in 76 patients evaluating the safety and efficacy of chronic oral flecainide therapy from Rotterdam, The Netherlands.
5. A compassionate use experience (8) using a 400 mg/day initial dose with upward titration at investigator discretion and primarily comprising 277 patients with lethal ventricular arrhythmias. This study will be called the "high initial dose compassionate study."
6. A study (9) in 429 patients with ventricular tachycardia treated in-hospital under monitored conditions with a 200 mg/day initial dose and slow upward titration. This study will be called the "low initial dose ventricular tachycardia study."
7. An open label safety and efficacy study in 86 patients with various forms of ventricular arrhythmias.
8. A postmarketing surveillance study in 155 patients conducted in the United Kingdom.

Stratification variables. Clinical strata of interest in assessing risk/benefit ratio were defined before retrospective data base analysis. Patients from this data base were stratified according to the severity of their underlying ventricular arrhythmia, classified into 1) those with premature ventricular complexes only, 2) those with nonsustained ventricular tachycardia, and 3) those with sustained ventricular tachycardia or ventricular fibrillation, or both. Sustained ventricular tachycardia was defined as ventricular tachycardia lasting 30 seconds or longer, requiring cardioversion or associated with hemodynamic consequences such as syncope or hypotension. Nonsustained ventricular tachycardia was defined as three or more consecutive ventricular complexes lasting less than 30 seconds and not associated with hemodynamic consequences.

The data base was further classified according to the presence or absence of structural heart disease. Structural heart disease was considered to be present when a patient had atherosclerotic coronary artery disease, significant valvular heart disease, congenital heart disease, cardiomyopathy or the presence of a ventricular aneurysm or a history of previous cardiac surgery. Patients with cardiomegaly by chest X-ray film, echocardiography or cardiac catheterization were also considered to have structural heart disease. Patients categorized by investigators as having primary electrical heart disease or no apparent cause for the ventricular arrhythmia were considered to have no structural heart disease.

Patients were further classified as having received orally 200, 300, 400 or 600 mg/day of flecainide. Patients who received a dose of less than 200 mg/day were included in the 200 mg/day classification. No patient received more than 600 mg/day. Intermediate doses were rounded upward. The sample size for each total daily dose level was based on the number of patients who at any time while receiving flecainide were exposed to that total daily dose of the drug. Patients were counted more than once in the denominator if they were exposed to multiple doses of flecainide. They were counted in the numerator at the dose they were receiving when the adverse event occurred. An adverse event was attributed only to the dose of flecainide at which it occurred.

Patients were also categorized into those who received out-of-hospital or in-hospital initiation of flecainide therapy. Treatment was initiated outside the hospital in all patients in the flecainide-quinidine comparison study and its follow-up. Approximately 25% of patients in the open label safety and efficacy study and approximately 60% in the postmarketing surveillance study conducted in the United Kingdom began treatment with flecainide as outpatients. All other patients had inpatient initiation of flecainide.

Adverse cardiac events. The adverse cardiac events reviewed included occurrence of proarrhythmia, congestive heart failure and conduction disturbances. Proarrhythmic events were identified by a direct, retrospective questionnaire from each investigator concerning each patient entered into the previously cited studies before March 1983, or after that time (prospectively) by case report forms designed to specifically define proarrhythmic events. *Proarrhythmic events were classified into one of three categories:*

1. Those arrhythmic events that resulted in death.

2. Those events that were considered serious but nonlethal, defined as worsened ventricular arrhythmias that re-

quired immediate termination with drugs, overdrive pacing or cardioversion. If the proarrhythmic event was associated with hypotensive symptoms, it was also considered serious but nonlethal.

3. Other proarrhythmic events as judged by the investigator included those with an increase in premature ventricular complexes (using previously published criteria) (8), new or increased frequency of nonsustained ventricular tachycardia or new ventricular arrhythmias characterized by a change in configuration or rate (of ventricular tachycardia) but which did not result in worsening of symptoms as compared with baseline.

Congestive heart failure resulting in death or discontinuation of flecainide was also reviewed. This information was obtained from prospective data; investigators were specifically asked to assess patients for congestive heart failure, determine whether it was a new development or an exacerbation of a prior state and evaluate its impact on the patient's care.

All patients with documented conduction disturbances were reviewed. Disturbances considered to be important were defined as new advanced atrioventricular (AV) block (greater than first degree) or sinus node dysfunction with sinus pauses or arrest, junctional escape rhythms or new symptomatic sinus bradycardia as defined by the individual investigators.

All deaths in the data base were reviewed and the cause of death, whether drug-related or not, was categorized into the following: 1) noncardiac death; 2) death due to acute myocardial infarction documented by typical electrocardiogram and enzyme changes or autopsy, or both; 3) death due to congestive heart failure or low output states; 4) in-hospital sudden arrhythmic death; and 5) out-of-hospital sudden death.

Role of high versus low dosing schedule. Data from the 277 patients in the high initial dose compassionate study and data from the 429 patients in the low initial dose ventricular tachycardia study were displayed separately to define the effects of a different dosing regimen on the incidence of various cardiac events. Analysis of patient demographics, cardiac disease status and arrhythmia diagnoses confirmed that these two study populations were identical and differed only in the dosing regimens employed. The initial dose of flecainide used in the high initial dose compassionate study was 400 mg/day orally, with a maximum of 600 mg/day; no specific requirement was made as to dose escalation intervals, the need for cardiac monitoring or the use of flecainide plasma levels in guiding therapy. Conversely, patients enrolled in the low initial dose ventricular tachycardia study were required to be treated initially in the hospital under monitored conditions with the dose regimen starting at 200 mg/day and increasing, only if necessary, to a maximum of 400 mg/day, in doses of 50 mg twice daily at intervals no more frequent than every 4 days. Plasma monitoring was used to avoid plasma levels greater than 1.0 μg/ml. Because of this difference in dose recommendations, patients in the low initial dose ventricular tachycardia study tended to receive lower maintenance doses. Half of the patients in the high initial dose compassionate study received maintenance doses greater than 300 mg/day, whereas 80% of the patients in the ventricular tachycardia study were treated with 300 mg/day or less.

Time of occurrence of adverse events. These events were separated into those occurring within 14 days and those occurring more than 14 days after initiation of flecainide therapy. Events occurring within 14 days were of interest, because hospitalization during initiation of therapy might reduce the risk to the patient of any serious cardiac events that occurred. Full dose ranging, beginning at 100 mg every 12 hours with increments every 4 days to 150 and 200 mg doses may require up to 12 or more days of observation until the effective dose is achieved. This analysis was intended to identify groups of patients at risk of serious cardiac events early in therapy, so that appropriate recommendations could be made concerning who ought to be hospitalized during therapy initiation. Tentative recommendations were that patients should be hospitalized if they had a history of sustained ventricular tachycardia, evidence of symptomatic congestive heart failure or a history of sinus node dysfunction.

Data analysis. A logit approach was used to evaluate adverse cardiac events in terms of potential predictors for their association with the incidence of adverse cardiac events. For this analysis, the predictors considered were the presence or absence of structural heart disease and arrhythmia type. For the compassionate use and ventricular tachycardia study data, high or low initial starting dose was also considered as a potential predictor. The significance of each of these variables as a predictor of outcome, as well as the independence of these predictors, was assessed. It is evident that there may be other potential predictors that are not evaluated in this analysis. However, because of the relative infrequent occurrence of some of these adverse cardiac events, a model to assess numerous predictors was not feasible.

Results

Characteristics of study patients. The 1,330 patients in this data base have been followed up for a mean of 292 ± 393 days (range 1 to 1,843; median 104). Of these patients, 573 (43%) are still taking flecainide at a mean follow-up time of 506 ± 464 days (range 4 to 1,843). Of the remaining patients, 157 (12%) discontinued therapy because drug efficacy was inadequate and 145 (11%) died, 77 (9%) because of aggravation of arrhythmia, 19 (1.5%) because of congestive heart failure, 20 (1.5%) because of conduction changes and 216 (16%) because of other factors, such as completion of the study, nonqualification, poor com-

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Table 1. Patients in Data Base Stratified for Various Baseline Characteristics and Doses Received

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	132 (28.1%)	64 (13.6%)	28 (7.2%)	224 (16.8%)
Yes	338 (71.9%)	405 (86.4%)	363 (92.8%)	1,106 (83.2%)
Total	470 (100%)	469 (100%)	391 (100%)	1,330 (100.0%)
Total daily dose (mg)*				
200	260 (55.3%)	347 (74.0%)	301 (77.0%)	908 (68.3%)
300	142 (30.2%)	250 (53.3%)	195 (49.9%)	587 (44.1%)
400	324 (68.9%)	218 (46.5%)	160 (40.9%)	702 (52.8%)
600	44 (9.4%)	50 (10.7%)	25 (6.4%)	119 (8.9%)
Study				
High initial dose compassionate use study	59 (12.6%)	118 (25.2%)	100 (25.6%)	227 (17.1%)
Low initial dose VT study	27 (5.7%)	204 (43.5%)	198 (50.6%)	429 (32.3%)
Outpatient initiation of therapy	273	88	15	376

*Patients were included more than once if exposed to multiple flecainide dosages. PVC = premature ventricular complex; VT = ventricular tachycardia.

pliance, intercurrent illness, personal decision and loss to follow-up.

Table 1 details the number of patients in each baseline subgroup, defined by type of ventricular arrhythmia as it related to structural heart disease, total daily dose and outpatient-inpatient initiation of therapy. The patients were approximately equally grouped into those who were treated for premature ventricualr complexes alone (n = 470), nonsustained ventricular tachycardia (n = 469) or sustained ventricular tachycardia (n = 391). Approximately 80% of patients had structural heart disease, and approximately 75% had therapy initiated while they were inpatients. Almost 90% of patients in the data base received 400 mg/day or less of flecainide.

Proarrhythmia. Proarrhythmic events were recorded in 90 (6.8%) of the 1,330 patients in the data base. Table 2 shows that patients with sustained ventricular tachycardia had a much greater incidence (16.4%) of proarrhythmic events than did those with premature ventricular complexes (1.7%) or nonsustained ventricular tachycardia (3.8%). The patients with sustained ventricular tachycardia in the high initial dose compassionate study had twice the incidence of proarrhythmic events (26%) compared with the patients in the low initial dose study of ventricular tachycardia (13.1%). Analyses indicated that type of ventricular arrhythmia ($p \leq 0.01$) and initial flecainide dose ($p \leq 0.05$) were both significant independent predictors of proarrhythmic events.

Table 3 shows the incidence of possible or probable proarrhythmia-induced deaths that occurred in 13 patients (1.0%) in the entire group of 1,330. This table shows that no deaths occurred from proarrhythmia in patients treated for premature ventricular complexes. Only 1 death (0.2%) occurred among the 469 patients treated for nonsustained ventricular tachycardia. That death occurred in the high initial dose compassionate study (1 of 118 patients), whereas no deaths have occurred in the 204 patients treated for nonsustained ventricular tachycardia in the low initial dose ventricular tachycardia study. The patient with nonsustained ventricular tachycardia who died was an 80 year old man with severe coronary artery disease, New York Heart Association class III congestive heart failure and recent subendocardial myocardial infarction with pulmonary edema. Flecainide was begun at 200 mg/day and increased to 400 mg/day, with good control of ventricular arrhythmia. He was discharged home 9 days after starting flecainide and after 2 days of taking 400 mg/day. He returned to the emergency room on the evening of discharge with a wide irregular tachycardia without P waves that deteriorated into cardiogenic shock and death. The relation of flecainide (versus deteriorating ischemic heart disease) to the terminal arrhythmia was not clear.

In patients treated for sustained ventricular tachycardia, a 10% incidence (10 of 100 patients) of proarrhythmic death was noted in the high initial dose compassionate study; this

Table 2. Summary of All Proarrhythmic Events

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	4/132 (3.0%)	2/64 (3.1%)	2/28 (7.1%)	8/224 (3.6%)
Yes	4/338 (1.2%)	16/405 (4.0%)	62/363 (17.1%)	82/1,106 (7.4%)
Total	8/470 (1.7%)	18/469 (3.8%)	64/391 (16.4%)	90/1,330 (6.8%)
Study				
High initial dose compassionate use study	0/59 (0.0%)	2/118 (1.7%)	26/100 (26.0%)	28/277 (10.1%)
Low initial dose VT study	2/27 (7.4%)	6/204 (2.9%)	26/198 (13.1%)	34/429 (7.9%)

Abbreviations as in Table 1.

Table 3. Death From Proarrhythmic Events

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	0/132 (0.0%)	0/64 (0.0%)	0/28 (0.0%)	0/224 (0.0%)
Yes	0/338 (0.0%)	1/405 (0.2%)	12/363 (3.3%)	13/1,106 (1.2%)
Total	0/470 (0.0%)	1/469 (0.2%)	12/391 (3.1%)	13/1,330 (1.0%)
Study				
High initial dose compassionate use study	0/59 (0.0%)	1/118 (0.8%)	10/100 (10.0%)	11/277 (4.0%)
Low initial dose VT study	0/27 (0.0%)	0/204 (0.0%)	1/198 (0.5%)	1/429 (0.2%)

Abbreviations as in Table 1.

rate dropped to 0.5% (1 of 198 patients) in the low initial dose ventricular tachycardia study, a 20-fold decrease ($p < 0.01$). In fact, no patient in the latter study died of a proarrhythmic event in the subsequent 2 1/2 years before this data analysis. In the compassionate use and ventricular tachycardia studies, the type of arrhythmia ($p < 0.05$) and initial dose ($p < 0.01$) were found to be independent predictors for proarrhythmic death.

Table 4 shows the incidence of serious nonlethal proarrhythmic events. These occurred in 30 patients (2.3%), 29 of whom had structural heart disease. None of the patients treated for premature ventricular complexes developed a serious nonlethal proarrhythmic event. Of the four patients with nonsustained ventricular tachycardia who had a serious nonlethal proarrhythmic event, all had structural heart disease, three had congestive heart failure and two had depressed left ventricular ejection fraction (29 and 36%, respectively). In three of the patients, the proarrhythmic event resulted in syncope, and in the other resulted in a wide complex tachycardia that required cardioversion. Patients with sustained ventricular tachycardia had the highest incidence of serious nonlethal proarrhythmic events (6.6%).

Table 5 details other proarrhythmic events. The incidence of this form of proarrhythmia did not appear to be related to the presence or absence of structural heart disease but did correlate with the severity of the baseline arrhythmia. Patients with sustained ventricular tachycardia had the highest risk for this type of proarrhythmia.

Table 6 shows the relation of flecainide dose to types of proarrhythmic events that occurred in patients with sustained ventricular tachycardia. There was no consistent relation between dose and the incidence of proarrhythmic events of any type in patients treated for premature ventricular complexes only or for nonsustained ventricular tachycardia. These data demonstrate that there is a dose relation to all proarrhythmic events, to those resulting in death and to those of the serious nonlethal type in patients with sustained ventricular tachycardia receiving 200 to 400 mg/day of flecainide. The number of patients exposed to 600 mg/day is too small to draw meaningful conclusions about a relation.

Congestive heart failure. Of 1,330 patients, 6 (0.5%) died from congestive heart failure that might be attributed to flecainide and 19 had flecainide therapy discontinued after developing new or worsening congestive heart failure. All six patients who died had significant myocardial dysfunction before receiving flecainide. There was no relation between congestive heart failure and the dose of flecainide received. Four of the patients who died had a history of sustained and two had history of nonsustained ventricular tachycardia. Of the two patients with nonsustained ventricular tachycardia, one had a history of myocardial infarction with recent exacerbation of angina and an exacerbation of congestive heart failure 3 weeks before receiving flecainide. After receiving flecainide for 3 days, he developed increasingly severe congestive heart failure and died. The investigator believed that the sudden onset may have been caused by new ischemia and therefore a definite relation with flecainide could not be established. The second patient who had nonsustained ventricular tachycardia had coronary artery disease and an ejection fraction of 22%. He had done well with flecainide therapy for 3 months when signs of worsened congestive

Table 4. Serious Nonlethal Proarrhythmic Events

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	0/132 (0.0%)	0/64 (0.0%)	1/28 (3.6%)	1/224 (0.4%)
Yes	0/338 (0.0%)	4/405 (1.0%)	25/363 (6.9%)	29/1,106 (2.6%)
Total	0/470 (0.0%)	4/469 (0.9%)	26/391 (6.6%)	30/1,330 (2.3%)
Study				
High initial dose compassionate use study	0/59 (0.0%)	0/118 (0.0%)	8/100 (8.0%)	8/277 (2.9%)
Low initial dose VT study	0/27 (0.0%)	2/204 (1.0%)	12/198 (6.1%)	14/429 (3.3%)

Abbreviations as in Table 1.

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Table 5. Other Proarrhythmic Events

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	4/132 (3.0%)	2/64 (3.1%)	1/28 (3.6%)	7/224 (3.1%)
Yes	4/338 (1.2%)	11/405 (2.7%)	25/363 (6.9%)	40/1,106 (3.6%)
Total	8/470 (1.7%)	13/469 (2.8%)	26/391 (6.6%)	47/1,330 (3.5%)
Study				
High initial dose compassionate use study	0/59 (0.0%)	1/118 (0.8%)	8/100 (8.0%)	9/277 (3.2%)
Low initial dose VT study	2/27 (7.4%)	4/204 (2.0%)	13/198 (6.6%)	19/429 (4.4%)

Abbreviations as in Table 1.

heart failure developed. Despite a decreasing dosage of flecainide, he was admitted for uncompensated congestive heart failure 9 days later and died 1 week afterward of ventricular tachycardia, considered to be secondary to worsened congestive heart failure. The investigator stated that the death was probably not related to flecainide.

New or worsened congestive heart failure caused discontinuation of flecainide in 19 patients (1.4%). All 19 had structural heart disease and there was no relation between discontinuation for congestive heart failure and the type of underlying arrhythmia or dose of flecainide. Of the 19 patients, 3 (0.6%) of 470 were treated for premature ventricular complexes only, 10 (2.1%) of 469 for nonsustained ventricular tachycardia and 6 (1.5%) of 391 for sustained ventricular tachycardia. Ten (53%) of the 19 patients discontinued flecainide within 14 days of initiation of the dose. Two of these 10 had sustained ventricular tachycardia, and 6 had severe congestive heart failure with low ejection fraction; therefore, 8 of the 10 patients who had to discontinue therapy within 14 days would have received in-hospital initiation of flecainide. The other two patients who would not have received in-hospital initiation were treated for nonsustained ventricular tachycardia and developed symptoms of congestive heart failure as outpatients 7 and 11 days, respectively, after initiation of flecainide. Both responded to discontinuation of flecainide without requiring specific therapy for congestive heart failure.

Conduction disturbances. Significant conduction disturbances were reported in 29 (2.2%) of the 1,330 patients and none were fatal. The incidence of significant conduction disturbances was not related to the severity of the underlying arrhythmia, presence or absence of structural heart disease or dose of flecainide. Of these 29 patients, 11 developed symptoms associated with the conduction disturbances (dizziness, weakness or presyncope in 7 and syncope in 4). Table 7 details the symptomatic conduction disturbances by subgroups, and shows that the prevalence of these disturbances was not related to the type of ventricular arrhythmia treated or the total daily dose of drug.

Of the 29 patients who developed conduction disturbances, 20 discontinued flecainide and 9 continued taking the drug, 8 of whom received a permanent pacemaker. Before initiation of flecainide therapy, 19 of the 29 patients had known preexisting conduction disturbances. Of the four patients who developed syncope, two had known underlying sinus bradycardia due to sick sinus syndrome and the other two had sustained ventricular tachycardia and left bundle branch block at baseline. In all four cases the syncope that occurred when the patient was given flecainide was due to prolonged sinus pauses. No patient developed syncope because of the occurrence of AV node or His-Purkinje system complete heart block.

Deaths. Of the 1,330 patients receiving flecainide, 123 (9.7%) died. Both the presence of structural heart disease ($p \leq 0.01$) and the type of ventricular arrhythmia ($p \leq 0.05$) were found to be independent predictors of the incidence of death. The incidence of death in patients with sustained ventricular tachycardia (16.1%) was greater than that for patients with premature ventricular complexes (3.2%) or nonsustained ventricular tachycardia (9.6%). All but three of these deaths occurred in patients with structural heart disease. Of the three patients without structural heart dis-

Table 6. Relation of Flecainide Dose to Type of Proarrhythmic Events in Patients Treated for Sustained Ventricular Tachycardia

	All	Serious Nonlethal	Deaths
Total daily dose (mg)*			
200	14/301 (4.7%)	7/301 (2.3%)	0/301 (0.0%)
300	22/195 (11.3%)	9/195 (4.6%)	3/195 (1.5%)
400	24/160 (15.0%)	7/160 (4.4%)	8/160 (5.0%)
600	4/25 (16.0%)	3/25 (12.0%)	1/25 (0.5%)

*Patients were included more than once if exposed to multiple flecainide dosages.

Table 7. Symptomatic Conduction Disturbances

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	3/132 (2.3%)	0/64 (0.0%)	0/28 (0.0%)	3/224 (1.3%)
Yes	2/338 (0.6%)	2/405 (0.5%)	4/363 (1.1%)	8/1,106 (0.7%)
Total	5/470 (1.1%)	2/469 (0.4%)	4/391 (1.0%)	11/1,330 (0.8%)
Study				
High initial dose compassionate use study	0/59 (0.0%)	1/118 (0.8%)	4/100 (4.0%)	5/277 (1.8%)
Low initial dose VT study	0/27 (0.0%)	1/204 (0.5%)	0/198 (0.0%)	1/429 (0.2%)

Abbreviations as in Table 1.

ease, one died of metastatic carcinoma, one had unobserved sudden death at home after 7 months of flecainide therapy in which the cause of death was possible cerebral vascular accident secondary to hypertensive disease and the third patient had sudden cardiac death at home 16 days after initiation of flecainide but had a prior history of resuscitation from sudden cardiac death. All three of these patients had documented control of their ventricular arrhythmia while taking flecainide before death.

In-hospital arrhythmic death occurred in 42 patients (3.2%) and out-of-hospital sudden death in 49 patients (3.7%), which includes those deaths thought to be due to proarrhythmic events, as discussed earlier. All but two of these deaths occurred in patients with structural heart disease ($p < 0.05$) and there was a highly significant ($p < 0.05$) independent relation to the type of underlying ventricular arrhythmia (Table 8). There was no clear overall relation between dose of flecainide and sudden death, but there was a tendency for higher doses to be associated with sudden death in patients with sustained ventricular tachycardia. Patients treated in the high initial dose compassionate study had twice the mortality rate compared with those treated in the low initial dose ventricular tachycardia study.

Events within 14 days of initiation of therapy. The occurrence of adverse cardiac events and death was correlated with whether flecainide was initiated as inpatient or outpatient therapy, and how long after initiation these events occurred. No proarrhythmic death occurred when flecainide therapy was initiated in outpatients with premature ventricular complexes or nonsustained ventricular tachycardia. Fifteen patients in this database were exposed to flecainide as outpatients with the diagnosis of sustained ventricular tachycardia, and one (6.7%) had a proarrhythmic death.

Twelve of the 13 proarrhythmic deaths occurred within 14 days of initiation of flecainide, 11 in patients with sustained ventricular tachycardia and 1 in a patient with a nonsustained ventricular tachycardia plus class III congestive heart failure with an ejection fraction of less than 30%. All 12 patients would have been hospitalized if the recommendations for hospitalization had been followed (that is, hospitalize patients with sustained ventricular tachycardia, evidence of symptomatic congestive heart failure or history of sinus node dysfunction).

Among the 30 patients with a serious nonlethal proarrhythmic event, 23 events (77%) occurred within 14 days after initiation of flecainide therapy. All but one of these patients would have received in-hospital initiation of flecainide if recommended guidelines for such initiation had been used.

Three of the six deaths due to congestive heart failure occurred within 14 days of initiation of flecainide. All three would have had in-hospital initiation of treatment using the recommended criteria for inpatient initiation.

Of the four patients who developed syncope on flecainide, three experienced the event within 14 days of initiation of flecainide. One had been treated for sustained ventricular tachycardia and the other two had known sinus node dysfunction at baseline. All three, therefore, would have had

Table 8. In-Hospital Arrhythmic Deaths and Out-of-Hospital Sudden Deaths

	PVC Only	Nonsustained VT	Sustained VT	Total
Structural heart disease				
No	1/132 (0.8%)	0/64 (0.0%)	1/28 (3.6%)	2/224 (0.9%)
Yes	10/338 (3.0%)	30/405 (7.4%)	49/363 (13.5%)	89/1,106 (8.0%)
Total	11/470 (2.3%)	30/469 (6.4%)	50/391 (12.8%)	91/1,330 (6.8%)
Study				
High initial dose compassionate use study	4/59 (6.8%)	7/118 (5.9%)	20/100 (20.0%)	31/277 (11.2%)
Low initial dose VT study	0/27 (0.0%)	9/204 (4.4%)	18/198 (9.1%)	27/429 (6.3%)

Abbreviations as in Table 1.

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in-hospital initiation of flecainide based on the recommendation that patients with sinus node dysfunction or sustained ventricular tachycardia be initially treated as inpatients.

Thirty-seven patients with in- or out-of-hospital sudden death died within 14 days of initiation of flecainide therapy. Twenty-seven of these 37 patients were treated for sustained ventricular tachycardia and the other 10 had evidence of significant myocardial dysfunction. Therefore, all of these patients would have received in-hospital initiation of flecainide based on the recommendation for inpatient treatment.

Discussion

The data in this study were derived from a carefully recorded, prospectively determined set of trials of the new potent class IC antiarrhythmic agent flecainide acetate. This large data base can therefore serve as a means of defining relations among the classification of ventricular arrhythmias, dose rate of flecainide administration and the occurrence of serious adverse cardiac events.

Classification of arrhythmia versus efficacy and adverse events. Classification of patients with ventricular arrhythmias into those with 1) premature ventricular complexes only, 2) nonsustained ventricular tachycardia, and 3) sustained ventricular tachycardia has previously been demonstrated to provide useful correlations with the efficacy of flecainide (4–9). Among patients with premature ventricular complexes only and nonsustained ventricular tachycardia who were treated in placebo-controlled and quinidine comparative randomized trials (4–7), 80 to 90% of patients demonstrated excellent efficacy with flecainide. Conversely, among patients treated for sustained ventricular tachycardia using noninvasive or electrophysiologic approaches, or both, approximately 20 to 50% of patients responded to flecainide (9–11). This is a higher response rate than that seen with other class I antiarrhythmic agents (1,2).

This study defines the relative risk of serious adverse cardiac effects: proarrhythmia, congestive heart failure and conduction disturbances with flecainide therapy; it also shows that their incidence is correlated closely with the classification system used for ventricular arrhythmias (2,3). However, the development of symptomatic conduction disturbances is related to the electrophysiologic action of flecainide and is better predicted by the baseline sinus node function rather than by the class of ventricular arrhythmia before treatment.

Of the 470 patients treated for premature ventricular complexes only, there were no flecainide-related deaths, no serious proarrhythmic events and a low sudden cardiac death rate (2.3%). Among the 469 patients treated for nonsustained ventricular tachycardia, there was one possible proarrhythmic death, four serious nonlethal proarrhythmic events, two deaths due to congestive heart failure and a combined sudden death incidence in these patients of 6.4%.

Outpatient versus inpatient initiation of flecainide therapy. The data herein support the view that flecainide can be safely initiated in selected outpatients because the prevalence of serious adverse cardiac reactions is quite low. Obviously, more data are required to confirm these results with a higher level of confidence. Hospitalization is recommended for all patients with a history of sustained ventricular tachycardia when treated with any antiarrhythmic agent. For patients with less severe arrhythmias, hospitalization during initiation of flecainide therapy is recommended if they have symptomatic congestive heart failure or sinus node dysfunction. These characteristics were present in all but three of the patients treated for premature ventricular complexes or nonsustained ventricular tachycardia who died or had serious adverse cardiac experiences within 14 days of therapy. All 10 patients treated for premature ventricular complexes or nonsustained ventricular tachycardia who had in- or out-of-hospital sudden death within 14 days would have received in-hospital initiation of flecainide. Three of the four patients with serious proarrhythmic events would have been hospitalized. The remaining patient who was treated for nonsustained ventricular tachycardia reported to the emergency room with light-headedness and was found to have a wide complex tachycardia requiring cardioversion. Eight of the 10 patients treated for premature ventricular complexes or nonsustained ventricular tachycardia who required early discontinuation of flecainide because of congestive heart failure also would have been hospitalized. The two who would not have been hospitalized had only mild symptoms of congestive heart failure and required no therapy other than discontinuation of flecainide. Thus it is clear that all patients who might have benefited from hospitalization would be hospitalized if the present recommendations were followed.

Risk versus benefit of flecainide. Thus, the concern of benefit versus risk for the use of flecainide in patients with ventricular arrhythmias can be more clearly estimated by the data provided in this report. Although it is quite clear that patients benefit by elimination of hemodynamic or lifestyle–limiting symptoms when the severity of arrhythmia is reduced by the potent agent flecainide, it is still unknown whether sudden cardiac death in high risk patients is in fact prevented when antiarrhythmic agents are used to eliminate the major risk factor of ventricular arrhythmias. Very few data exist that analyze the serious adverse cardiac reactions using other antiarrhythmic drugs in relation to the nature of the patients being treated and the characteristics of their ventricular arrhythmias. We do know, for example, that initiating quinidine therapy in outpatients with benign or potentially lethal ventricular arrhythmias similarly has a very low incidence of proarrhythmia (about 6%) and no deaths, as was also seen in this study using flecainide (12). A much higher prevalence of proarrhythmia, and particularly the presence of torsade de pointes, is mostly seen in patients

treated with quinidine who manifest atrial fibrillation, congestive heart failure or hypokalemia.

Thus, it appears that it is more important to understand the clinical conditions associated with the arrhythmia rather than the arrhythmia itself if one wishes to predict the potential for serious adverse cardiac reaction due to antiarrhythmic drug therapy. We therefore recommend for flecainide, as for other antiarrhythmic agents, in-hospital initiation of therapy for patients with sustained ventricular tachycardia, serious compromised left ventricular function (particularly with symptomatic congestive heart failure) and unstable cardiac states, such as unstable ischemia and electrolyte imbalance (particularly hypokalemia). Patients with sick sinus syndrome are at risk of developing higher degrees of block from potent antiarrhythmic drugs such as flecainide, and therefore in all such patients such therapy should be initiated in the hospital.

Clinical use of flecainide in serious cases. The data comparing the high initial dose compassionate study and the low initial dose ventricular tachycardia study demonstrate clearly the principle that the seriously ill patient with sustained ventricular tachycardia must be treated not only in the hospital, but also with a careful dosage regimen, starting with a small total daily dose of the drug and not increasing that dose until steady state has been reached. Initiating therapy with a lower dose of flecainide at 100 mg twice a day is a safety precaution that should be followed for all patients to be treated because this agent is so potent and higher doses are often not needed. Thus, a regimen for flecainide using an initial dose of 100 mg twice a day with incremental increases of 50 mg twice a day every 4 days under careful monitoring of both the electrocardiogram and blood levels has markedly reduced the prevalence of serious proarrhythmia, congestive heart failure and death. Patients rarely require more than 200 mg twice a day when lethal ventricular arrhythmias are present, whereas up to 600 mg/day of flecainide has been found to slightly increase the rate of successful treatment in patients with benign or potentially lethal ventricular arrhythmias whose treatment is initiated outside the hospital (4–7).

Conclusions. It is not only the form of the ventricular arrhythmia, but also the accompanying clinical characteristics, that determine the predictability of serious adverse cardiac reactions to antiarrhythmic drugs. The classification of patients with ventricular arrhythmias into those with premature ventricular complexes, nonsustained ventricular tachycardia and sustained ventricular tachycardia can be used not only to predict the efficacy rates of flecainide and other antiarrhythmic agents, but also the ability to predict serious adverse cardiac events. The use of this classification system to report antiarrhythmic drug trial efficacy and safety results and to define patients for sudden cardiac death prevention trials seems warranted.

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