Table 19 summarizes some drug interaction data reviewed by Marcus (1983) and dosage reduction recommendations.

TABLE 19 EFFECTS OF AMIODARONE ON OTHER DRUGS

	Interaction			
Concomitant Drug	Onset (days)	Magnitude of Effect	Duration	Recommended Dose Correction for Concomitant Drug
Warfarin	3 to 4	Increases prothrombin time by 100%	2 wk to 4 mo	↓1/3
Digoxin	1	Increases serum concentration by 70%	2 wk	↓1/2
Quinidine	2	Increases serum concentration by 33%	?	↓1/3 (or avoid)
Procainamide	less than 7	Increase plasma concentration by 55%, NAPA concentration by 33%	?	↓1/3 (or avoid)

NAPA = N-acetylprocainamide (Marcus, 1983)

In the Detailed Study and the Global Survey conducted by Ives (see section VI), interactions with amiodarone were reported in a total of 32 of 97 (33%) patients receiving oral anticoagulants, 58 of 346 (17%) patients receiving digoxin and 22 of 344 (6%) patients receiving other antiarrhythmic drugs Interactions with warfarin were predominantly elevation of prothrombin time, 9 patients had clinical toxicity including bruising, bleeding, and 2 deaths (subdural hematoma and subarachnoid hemorrhage) which may have been related to the interaction Amiodarone-digoxin interactions were most frequently reflected in an increase in serum digoxin level. Thirteen patients had symptoms of digoxin toxicity including one case of fatal, refractory bradycardia and one case of cardiac arrest

Amiodarone, administered in combination with other antiarrhythmics, produced elevated serum levels of these agents and in several patients resulted in worsening of neurological, gastrointestinal and cardiovascular side effects Two patients had fatal arrhythmias (ventricular tachycardia and fibrillation) possibly related to amiodarone interactions with quinidine and procainamide

The results of Ives' studies thus support observations in the literature that potentially serious interactions may occur when amiodarone is administered with various other drugs. In fact, as investigators in Ives' studies presumably adjusted doses of concomitant medications in anticipation of such interactions, the incidence of reported interactions in the Detailed Study and Global Survey is almost certainly lower than would actually occur if no dose changes were made.

VI CLINICAL EXPERIENCE EFFICACY

A Introduction

The clinical evaluation of amiodarone has not followed the usual course Although the drug was developed in the early 1970's and was marketed in a number of countries, the drug's owner, Sanofi of Belgium, had no U S commercial interest and never sponsored an IND for the drug Interest in the drug grew rapidly in the late 1970's and early 1980's and numerous (hundreds of) individual investigators did obtain INDs to treat patients who had exhausted alternative antiarrhythmic agents Sanofi supplied the drug but had no role in protocol development or data collection or evaluation. Nonetheless, as a vast literature attests, the U S. and foreign cardiology communities have used and studied the drug extensively, not in so orderly a fashion as would be useful for a commercial sponsor, but, in the end, very thoroughly, at least for use of the drug in life-threatening arrhythmias. The difficulty has been how to gain access to these data

Fortunately, a commercial interest did develop in the form of Ives Laboratories, Inc., which agreed to extract the needed data from the available experience. The approach taken was to examine for effectiveness and common adverse events the entire amiodarone experience of several investigators and to examine for more serious adverse effects essentially all investigators focusing on patients who died or stopped amiodarone because of an adverse event. Ives thus carried out two retrospective studies to support the efficacy and safety of amiodarone for the treatment of cardiac arrhythmias These studies, based on U S clinical experience, were as follows

Detailed study of safety and efficacy

For the Detailed Study it was essential that an unselected population be examined Therefore, 50 consecutive patients receiving amiodarone in each of 4 major U S medical centers and all 41 patients from a fifth center (total of 241 patients) were evaluated in terms of antiarrhythmic response, adverse effects, and dosing regimens. For the Detailed Study, Ives' medical staff conducted site visits to transpose detailed information from original medical-hospital records to case report forms prepared by Ives Data were collected between November 1982 and January 1983

Global Survey

A broader search was needed for serious adverse effects. One hundred ninety-four IND holders, 80% of the total of 242 as of September 1982, responded to Ives' postal survey in December 1982. Of the total of 4802 patients these investigators had treated with amiodarone at that time, safety details were provided for the 1024 patients who had either discontinued amiodarone because of adverse effects (N=399) or died while receiving amiodarone (N=625).

Efficacy results of the two studies and of supportive U S and foreign studies are discussed below. These studies were not statistically analyzed because

1 studies were open-label and retrospective,
2 no comparative antiarrhythmic drugs were used,
3 each center followed a different dosage regimen and used its own assessment schedule,
4 baseline data, when available, were frequently obtained while patients were still on prior antiarrhythmic therapy, or were obtained prior to adequate washout of previous therapy (often necessary because of the severity of the underlying arrhythmia)

Since these studies were carried out, many individual investigators have reported on their experience with amiodarone, so that the conclusions of the Ives studies can be compared with a variety of other data bases

B. Detailed Study

Five major U S medical centers were selected because of a large amiodarone experience and because the principal investigators had extensive experience in the treatment of arrhythmias, and in the use of amiodarone. Patients were generally referred to these centers for treatment of serious, refractory arrhythmias. The five investigators were

John Fisher, M D
Montefiore Hospital and Medical Center
111 East 210th Street
Bronx, NY 10467

Charles Haffajee, M D.
University of Massachusetts Medical Center
55 Lake Avenue North
Worcester, MA 01605

Louis Rakita, M.D.
Cleveland Metropolitan General Hospital
3395 Scranton Road
Cleveland, OH 44109

Bramah Singh, M.D., D.Phil.
Wadsworth VA Hospital
Wilshire and Sawtelle Blvds.
Los Angeles, CA 90073

Douglas Zipes, M.D.
Indiana University School of Medicine
110 West Michigan Street
Indianapolis, IN 46202

Fifty consecutive patients in each of 4 centers and all 41 in one center (Dr. Fisher) were identified, without regard to the type of arrhythmia treated or the amount or quality of the data available. While this procedure eliminated bias in terms of antiarrhythmic response (efficacy) and safety, it did not assure that the best documented patients were available for quantitative assessment (i.e., there were absent baseline and treatment Holter recordings, rhythm strips, etc. in some patients). An inevitable limitation of the study was that the results are based on the investigators' dosage regimens and methods of assessment at the time of the study (November 1982 to January 1983), with subsequent experience the dosage recommendations and guidelines for following patients have been modified. By studying 5 centers, each using slightly different regimens for dosage and evaluation, a range of patient reponses (efficacy and safety) are available from each center as well as from the pooled data.

1 Patient Description

Demographic characteristics of the 241 patients are presented in Table 20

TABLE 20 PATIENT DEMOGRAPHICS

	Fisher	Haffajee	Rakita	Singh	Zipes	Pooled
No. Pts.	41	50	50	50	50	241
Age (yrs)						
mean	59.8	58 7	60.6	57.6	55.6	58.4
range	34-81	22-84	34-78	25-77	26-77	22-84
Sex						
male	29 (71%)	36 (72%)	36 (72%)	46 (92%)	38 (76%)	185 (77%)
female	12 (29%)	14 (28%)	14 (28%)	4 (8%)	12 (24%)	56 (23%)
Weight (lbs)						
mean	60 7	181.0	167 0	178.9	169.1	171 3
range	100-235	110-230	100-243	89-320	104-227	89-320

The patients had significant cardiovascular disease as shown by diagnosis, left ventricular ejection fraction (LVEF) and prior antiarrhythmic therapy in Table 21.

TABLE 21 CARDIOVASCULAR HISTORY

	Fisher (N=41)	Haffajee (N=50)	Rakita (N=50)	Singh (N=50)	Zipes (N=50)	Pooled (N=241)
% Pts with						
Syncope	70	26	24	14	34	33
CHF	63	48	60	36	34	51
MI	61	48	42	28	44	43
Cardiomeg	71	46	36	28	18	38
Mean % LVEF (No pts.)	30 4 (19)	40 3 (33)	39 5 (20)	39 1 (33)	27 3 (16)	36 6 (121)
Mean No prior Antiarr Rx	4.7	2.5	3 8	2 0	3 6	3 3

LVEF - Left ventricular ejection fraction.

Dr. Fisher's center had a higher percentage of patients with a prior history of syncope, congestive heart failure, myocardial infarction and cardiomegaly and also a higher number of antiarrhythmic drug trials prior to initiating amiodarone therapy. Generally, patients were given amiodarone after an average of 3 (range 0 to 10) standard or investigational antiarrhythmic agents were withdrawn due to lack of efficacy and/or intolerable side effects. Only 1 patient received amiodarone without a trial of other antiarrhythmic therapy, therefore both ventricular and supraventricular patients began amiodarone because investigators were unable to identify other effective and well-tolerated antiarrhythmic agents

As expected, patients treated for ventricular arrhythmias had more significant underlying cardiac disease than patients treated for supraventricular arrhythmias Table 22 highlights these differences

Dr. Fisher treated only 1 patient for SVA, consistent with the more severe cardiovascular disease profile shown previously

TABLE 22· CARDIOVASCULAR HISTORY ACCORDING TO ARRHYTHMIA

		Percent of Patients with Cardiovascular History.					
Arrhythmia	Total Pts.	CHF	IHD	CMO	CMG	SYNC	Mean % LVEF (No. Pts.)
Ventricular	192	58%	73%	31%	52%	38%	34.3 (104)
Supraventricular	49	24%	18%	27%	22%	14%	49.9 (17)
All Patients	241	51%	61%	30%	46%	33%	36.6 (121)

CHF - Congestive Heart Failure, IHD - Ischemic Heart Disease, CMO - Cardiomyopathy, CMG - Cardiomegaly, SYNC - Syncope

The primary arrhythmias for which amiodarone was administered are listed in Table 23.

TABLE 23 PRIMARY ARRHYTHMIAS

Primary Arrhythmia	Fisher	Haffajee	Rakita	Singh	Zipes	Pooled
VF	0	1	0	2	2	5
VF/VT	7	13	10	9	16	55
VT/Sync	25	5	7	3	10	50
VT	8	13	31	13	16	81
VEB	0	0	0	1	0	1
SVA	1	18	2	22	6	49
TOTAL	41	50	50	50	50	241

VF - ventricular fibrillation, VT - ventricular tachycardia, SYNC - syncope, VEB - ventricular ectopic beats, SVA - supraventricular arrhythmia

Many patients had more than one arrhythmia, the primary indication for treatment was considered on the basis of severity or by listings provided by the investigator Only the response of the primary arrhythmia was assessed In subsequent listings, "VF" and "VF/VT" are combined as "VF" Ventricular tachycardia was not further subdivided into "sustained" and "nonsustained" However, it is likely that most patients had sustained VT in view of the resistant arrhythmias referred to by the 5 centers

The above tabulations show that amiodarone was used most often (about 80%) in patients with severe ventricular arrhythmias Two investigators, Dr Haffajee and Dr Singh, contributed the majority (40/49) of patients who received amiodarone for SVA. These patients had intolerable symptoms or hemodynamic complications resulting from resistant supraventricular tachyarrhythmias

The 49 patients with SVA included 11 with supraventricular tachycardia, 12 with atrial fibrillation, 6 with atrial flutter, 8 with atrial fibrillation/flutter and 12 with other combinations of SVA

There were 9 patients with Wolff-Parkinson-White syndrome, 1 had VF/VT, 1 VT and 7 SVA

2 Study Methodology

The studies were open-label, retrospective, with the patients acting as their own controls Baseline arrhythmias were documented on 24-hour ambulatory ECG recordings, continuous ECG and, in some patients, by pro rammed electrical stimulation Frequently, because of the severity of the arrhythmia and urgent need for treatment, baseline data were obtained while patients were on prior antiarrhythmic therapy, which would presumably cause the baseline status to be more favorable, documentation of arrhythmias immediately prior to amiodarone was not always available All patients with serious arrhythmias (usually VF and VT) or recurrent arrhythmias producing CHF, ischemic pain, syncope or intolerable palpitations, who were unresponsive to, or intolerant of, other antiarrhythmic agents, were considered for amiodarone therapy Patients were not excluded because of cardiovascular impairment (CHF, bradycardia) or concomitant medications, although closer observation and reduced doses were indicated in some cases

Therapy was initiated in hospital with continuous monitoring until risk of VF/symptomatic VT had abated Patients were discharged when their arrhythmia was satisfactorily controlled Subsequent outpatient visits were at intervals of 2 weeks to 3 months, depending on the primary arrhythmia, response and duration of therapy Safety monitoring is described in Section VII

Loading doses were generally 800 to 1600 mg daily (occasionally up to 2000 mg/day for repetitive VT/VF), administered in divided doses. (As indicated in Section V A.9.e, high loading doses are necessary for reasonably prompt attainment of antiarrhythmic effect, but dose-related neurologic and gastrointestinal ADR limit the size of the loading dose) After 1 to 2 weeks, depending on the primary arrhythmia, response and size of the loading dose, the dose was reduced (after an intermediate phase) generally to 200-400 mg per day (occasionally 600-800 mg/day for symptomatic VT or VF) Transition from loading to maintenance dose was sometimes made in 2 stages with the first reduction after 1 to 3 weeks, followed by a second decrease after 1 to 3 months At the time the study was conducted, two investigators, Drs Fisher and Zipes, did not consistently reduce maintenance doses below 600 mg per day unless significant adverse effects were present Dr Haffajee adjusted maintenance doses to achieve amiodarone plasma levels of 1 to 2 mg/l Only 2 investigators, Drs. Singh and Rakita, attempted routinely to reduce maintenance doses to 400 mg or less per day, utilizing Holter recordings to assess response With such divergent dosing schedules, it was not possible to define precisely a minimum effective dose

Response was assessed by continuous monitoring during the initial stage of therapy, followed by 24-hour ambulatory Holter recordings, and occasionally electrophysiologic studies (Often only qualitative rather than quantitative Holter results were available) Holters were performed most frequently by Dr Rakita, weekly records were obtained after dose changes, and upon appearance of complex ventricular activity dose was increased

3 Criteria for Response

For each patient, investigators provided an overall assessment of response to amiodarone Similarly, assessment was listed for each visit, and potentially reflected dose changes, intercurrent illnesses, etc Efficacy in patients treated for ventricular arrhythmias was always based on continuous ECG or ambulatory 24-hour Holter monitoring, response was predominantly based on the presence of VF (rare), VT or complex VEB on such recordings. Reduction in total VEB and elimination of syncope, symptomatic recurrences or hospitalizations for arrhythmia were also considered (Elimination of VT and reduction in complex VEB are probably a more significant indication of response than a decrease in total VEB) The criteria for assessing response of ventricular arrhythmias that were used by the 5 investigators were as follows

Effective Elimination by amiodarone alone of VF, VT and complex VEB and/or reduction in total VEB greater than 95%. (Some investigators accepted infrequent, asymptomatic episodes of VT which occurred at a slower rate and longer cycle length as compared to baseline.)

Partially Effective Need for second antiarrhythmic agent to achieve the above response, or only 50-95% reduction in total VEB.

Ineffective No improvement or worsening of arrhythmia.

The response of supraventricular arrhythmias was assessed primarily on the basis of symptoms (CHF, angina, palpitations, syncope, near-syncope) associated with the tachyarrhythmia The 5 investigators, reflecting the general approach of cardiologists, performed Holter recordings only infrequently in SVA patients. The criteria by which SVA response was assessed were as follows

Effective Complete relief of symptoms by amiodarone alone No hospitalization for arrhythmia.

Partially Effective. Marked improvement in symptoms on amiodarone alone and/or requirement for additional antiarrhythmic agents. No hospitalization for arrhythmia.

Ineffective No improvement or worsening of symptoms

These criteria were used by the 5 investigators to designate per visit and overall efficacy ratings. Although there was variation in specific management and amount and type of documentation available among the centers, the common efficacy criteria permit some conclusions regarding response to amiodarone.

4. Results Detailed Study

The Detailed Study evaluated patients with resistant, often life-threatening arrhythmias in a retrospective, open-label design, using the patient as his own control Although the study lacks the randomization and blinding features of the usual well-designed crossover study, it is a convincing, well-controlled trial nonetheless, providing convincing evidence for antiarrhythmic efficacy in ventricular and supraventricular arrhythmias Several aspects of the study are particularly convincing

a) Arrnythmia response of patients to temporary discontinuation of therapy, necessitated by ADR or other reasons. Twenty-four patients, 18 with ventricular and 6 with supraventricular arrhythmias, had observations prior to amiodarone, on therapy, off therapy and again, on amiodarone.

b) Arrnythmia response of patients to amiodarone dose reduction. One hundred twelve patients, 84 with ventricular and 28 with supraventricular arrhytnmias, had observations prior to therapy, on a stable amiodarone maintenance dose and then on a reduced maintenance dose, some patients had additional observations subsequent to dose increase Depending on duration of therapy before dose reduction, and the magnitude and duration of dose reduction, this experience can be similar to temporary discontinuation of therapy

c) Response of a major symptom, syncope, to amiodarone therapy Eighty patients, 73 with ventricular and 7 with supraventricular arrhythmias, had a history of syncope, presumably related to their underlying arrhythmia.

Results in the Detailed Study will be presented first for the above 3 pivotal subgroups. Then overall efficacy assessment in all 241 patients, Holter results of ventricular arrhythmias and mortality (total and arrnythmia) will be discussed.

a Results of Temporary Discontinuation of Therapy

The responses of all patients who temporarily discontinued amiodarone were evaluated in detail This subset of patients could be considered to have the best controlled observations, as they allow comparison of responses on therapy, off therapy and again on therapy. (Of course, it can be expected that most patients with such a pattern will have shown return of arrnythmia after discontinuation, otherwise the drug would not usually be resumed) Twenty-four patients had such a temporary interruption (greater than 2 weeks) in maintenance therapy, in 14 cases, medication was discontinued for ADR (see discussion in Section VII B) Among these 24 patients, control of arrhythmias was full, partial and unknown in 19, 3 and 2, respectively, prior to discontinuation

The response to discontinuing therapy is listed in Table 24.

TABLE 24. ARRHYTHMIA RESPONSE TO DISCONTINUATION OF AMIODARONE

Primary Arrhythmia	Total No. Pts.	No. (%) Pts. with Recurrence	Arrhythmias off Amiodarone (No. Pts.)
VF	5	3 (60)	VF (1), VEB (2)
VT/Sync	4	2 (50)	VT (2)
VT	9	8 (89)	VT (8)
SVA	6	6 (100)	SVA (4), VEB (2)
Total	24	19 (79)	----

The specific arrhythmias observed to recur were generally the same as the underlying arrhythmias for which amiodarone was originally administered. In 2 patients treated for VF and 2 treated for SVA, VEB were considered the "recurring" arrhythmia, a weak basis for a "recurrence" conclusion, although even in these 4 cases, VEB may have been frequent or complex and therefore considered to be a "warning" arrhythmia. (In particular, Dr. Rakita often reinstituted therapy when frequent, complex VEB first appeared). While off amiodarone, 1 patient had VF and cardiac arrest and 1 was hospitalized for VT, another patient was hospitalized for VT shortly after restarting amiodarone Thus of the 18 patients with VT/VF, 11 redeveloped their severe arrhythmia when amiodarone was stopped and 2 others might have been about to do so

Among the 19 patients with recurrence, control was known to have been reestablished in 18, including 11 of the 12 patients with VT/VF in whom the outcome was known, as shown in Table 25

TABLE 25 ARRHYTHMIA RESPONSE TO RESUMING AMIODARONE

Primary Arrhythmia	Total Pts. Restarted	Control of Arrhythmia After Restarting Amiodarone		
		Full	Partial	Unknown
VF	3	1	1	1
VT with syncope	2	2	0	0
VT	8	8	0	0
SVA	6	5	1	0
TOTAL	19	16	2	1

Duration of time off amiodarone was related to recurrence, as shown in Table 26.

TABLE 26 ARRHYTHMIA RECURRENCE ACCORDING TO DURATION OFF THERAPY

Arrhythmia	Duration (Mo) Off Amiodarone		
	All Pts.	Recurrence	No Recurrence
VF	1 5 (5)	2 1 (3)	0.6 (2)
VT with syncope	0 9 (4)	1 2 (2)	0.5 (2)
VT	3 1 (9)	3 4 (8)	0.5 (1)
SVA	3 4 (6)	3 4 (6)	0
TOTAL	2 5 (24)	3 0 (19)	0.5 (5)

Number of patients in parentheses

The 19 patients with arrhythmia recurrence were thus off amiodarone for a longer period of time than patients without arrhythmia recurrence (3 0 vs. 0.5 months) In view of the terminal half-life of amiodarone, it is likely that a longer period of observation off therapy would yield an even higher rate of arrhythmia recurrence From the above data, it is not possible to draw any conclusions regarding differences in rate of recurrence of specific arrhythmias.

The mean daily dose of amiodarone immediately prior to discontinuation was similar in the 19 patients with recurrence (399 mg/day) and the 5 patients without recurrence (420 mg/day) Furthermore, the mean total cumulative dose prior to discontinuing therapy was similar in patients with (148 g) and without (158 g) recurrence Among the 19 patients who resumed amiodarone because of arrhythmia recurrence, the mean total daily doses immediately prior to discontinuing therapy (399 mg/day) and upon resuming therapy (402 mg/day) were similar The 19 patients with recurrence were treated for a total duration of 342 and 414 days before and after, respectively, temporarily discontinuing therapy. The 5 patients without recurrence were treated for 177 and 337 days before and after interruption of therapy, respectively

Investigators generally resumed treatment at a dose known to be previously effective, rather than slowly proceeding through dose titration, particularly in patients with a history of symptomatic ventricular arrhythmias.

Therefore, in a group of patients with ventricular and supraventricular arrhythmias who served as their own control while on-off-on amiodarone, 79% had recurrence of arrhythmia while off amiodarone, generally redeveloping the same arrhythmia as had been treated initially. In a few cases, what were thought to be "warning" arrhythmias were observed and, in the patient care setting, were sufficient grounds for reinstitution of amiodarone. These findings, essentially a double crossover, while not constituting the optimal randomized design and certainly biased in favor of finding patients whose arrhythmia recurred when the drug was stopped, persuasively document the antiarrhythmic effects of amiodarone, serious, resistant arrhythmias were present before amiodarone, responded to treatment, recurred with discontinuation of therapy and again responded to administration of amiodarone. The recurrence rate would probably have been higher if patients without recurrence were observed longer than a mean of 2 weeks. Following a brief interruption of therapy, control was reestablished by resuming the previous dose. Had the interruptions been longer, it is possible that higher doses would have been required, essentially "reloading" to establish effective tissue concentrations.

b. Results of Dose Reduction

Of the 241 patients treated with amiodarone, 112 (84 with VA and 28 with SVA) had a reduction in amiodarone maintenance dose for 2 weeks or longer after a period of stability. In 35 of the 112 patients, amiodarone dose was reduced because of side effects (refer to Sect - VII.B, Dose Reduction)

Subsequent to dose reduction, 28 patients (25%) had recurrence of arrhythmia, 76 (68%) had no recurrence and the outcome was unknown in 8 patients (7%). Recurrence was generally assessed in terms of VT and VEB on Holter recordings, although only 20 patients had Holter documentation available. There were no observed recurrences of VF. As with response to temporary interruption of therapy, "recurrence" was sometimes said to have developed with the appearance of "warning arrhythmias" (frequent, complex VEB). Recurrence of SVA was assessed primarily in terms of symptoms associated with the tachyarrhythmia.

Recurrence of arrhythmia is shown in Table 27

TABLE 27 RECURRENCE OF ARRHYTHMIA FOLLOWING DOSE REDUCTION

Primary Arrnytnmia	Total Pts.	No. (%) Pts. With Recurrence	No. (%) Pts. Witn No Recurrence	Pts. With Unknown Response
VF	28	4 (14)	20 (71)	4 (14)
VT with syncope	21	5 (24)	16 (76)	0
VT	35	13 (37)	20 (57)	2 (6)
SVA	28	6 (21)	20 (71)	2 (7)
Total	112	28 (25)	76 (68)	8 (7)

Duration of therapy, total daily dose (TDD) and cumulative dose in patients with and without recurrence are listed in Table 28

TABLE 28 DOSE AND DURATION OF THERAPY ACCORDING TO ARRHYTHMIA RESPONSE

	Arrnytnmia Recurrence	No Arrnythmia Recurrence
	(N=28)	(N=76)
Mean duration of therapy before dose reduction (days)		
Total	549	594
At dose immediately before |	247	213
Mean duration of therapy after dose reduction (days)		
Total	446	360
At dose immediately after |	144	267
Mean TDD (mg/day)		
Before dose |	549	594
After dose |	337	340
Mean cumulative dose		
Before dose | (g)	135	135

Mean total cumulative dose prior to dose reduction was slightly higher in the 76 patients witnout recurrence (135 g) than in the 28 patients with arrnytnmia recurrence (105 g)

The amiodarone dose was subsequently increased in 30 patients (28 with arrhythmia recurrence and 2 with unknown responses to dose reduction who most likely also had recurrence). Among the 30 patients, full (20) or partial (2) control was regained in 22 cases, the response of 8 patients was unknown. The 22 patients with known response had amiodarone doses increased approximately to their initial doses (Table 29).

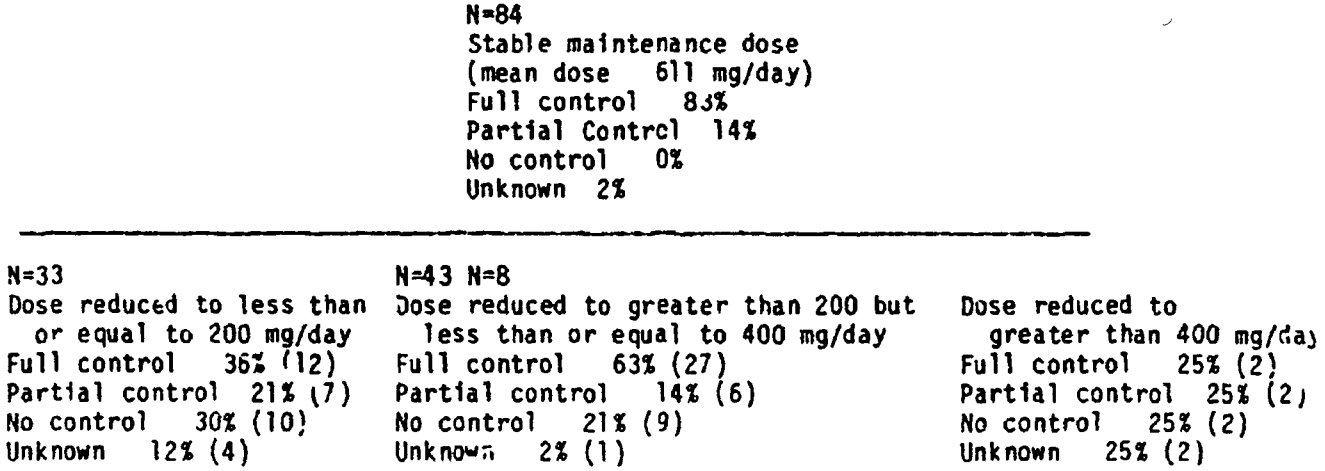
TABLE 29 MEAN TOTAL DAILY DOSE (TDD) IN PATIENTS WHO REGAINED CONTROL

Dose (mg/day)	Ventricular Arrhythmias (N=16)	Supraventricular Arrhythmias (N=6)
Original *	525	467
Reduced+	300	241
Final*	562	500

* Arrhythmia controlled
\+ Arrhythmia recurred

Results of dose reduction in the 84 patients with ventricular arrhythmias are shown in Figure 12.

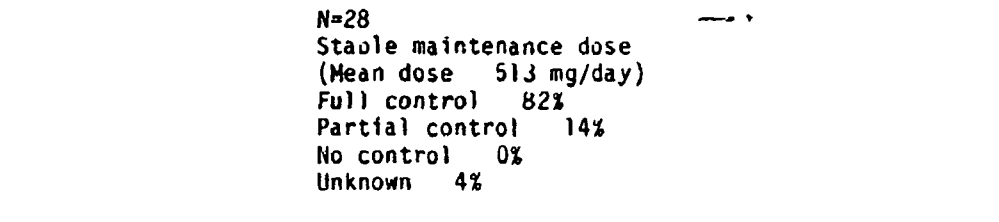
FIGURE 12 RESPONSE OF VENTRICULAR ARRHYTHMIAS TO DOSE REDUCTION



Following dose reduction, arrhythmia control was maintained better on 400 mg/day or more than on less than 400 mg/day (full or partial control in 73%, i.e., 37/51, vs 58% or 19/33).

Figure 13 illustrates the response of supraventricular arrhythmias.

FIGURE 13 RESPONSE OF SUPRAVENTRICULAR ARRHYTHMIAS TO DOSE REDUCTION



In patients with supraventricular arrhythmias, 70% or more of patients remained fully or partially controlled on doses of 200 mg/day or less.

As with the observations during temporary interruption of therapy, arrhythmia recurrence in 25% of patients following amiodarone dose reduction and reestablishment of control with dose increase provides further demonstration of the drug's antiarrhythmic properties in ventricular and supraventricular arrhythmias. Likelihood of arrhythmia recurrence in an individual patient may depend on underlying arrhythmia and cardiovascular disease, magnitude of dose reduction, total duration of therapy, as well as duration on the specific dose level immediately prior to reduction

The data indicate that when the daily maintenance dose was reduced to 400 mg there was usually no recurrence of the ventricular arrhythmias Some patients with these arrhythmias were controlled on doses of less than 400 mg/day In contrast, supraventricular arrhythmias responded similarly to doses less than or equal to 200 mg per day and to 300-400 mg per day Interpretation of the above

data is limited for several reasons 1) there was not a uniform schedule for dose reduction, and 2) some patients who failed on the initial attempt at dose reduction resumed a higher dose but were later successfully controlled at a reduced dose (often, the same dose that was previously inadequate).

Despite the difficulties inherent in a retrospective study of this type, the return of some arrhythmias on dose reduction indicates that they were being controlled by amiodarone The fact that more recurrence was seen with greater dose reductions further supports this It also indicates that a dose reduction to a daily maintenance dose of 400 mg usually does not lead to recurrence Some patients with ventricular arrhythmias may be controlled on doses of less than 400 mg/day

c Response of Syncope

Eighty patients had a history of syncope prior to amiodarone therapy Among these, 73 patients were treated for ventricular arrhythmias (VF in 23, VT in 50) and 7 for supraventricular arrhythmias. In this group of patients, it was assumed that syncope was a manifestation of VF or VT with hypotension (in supraventricular arrhythmias, patients may have had hypotension with SVT or a separate ventricular arrhythmia) In patients with quantitative data available, a range of 1 to 4 episodes of syncope was listed

During amiodarone therapy (mean duration 434 days), none of these 80 patients was hospitalized for syncope and only one experienced presyncope without documentation of an accompanying arrhythmia or bradycardia

Although this aspect of the study was also uncontrolled, the complete absence of syncope in this patient population provides important evidence for the efficacy of amiodarone

d Overall Efficacy Assessment by Investigators

Additional support for the efficacy of amiodarone can be derived from the overall efficacy assessments made by the investigators

The efficacy response of the 241 patients, according to criteria described in Section 2 3, is listed by arrhythmia in Table 30

TABLE 30 RESPONSE TO AMIODARONE

Primary Arrnytnmia	Total Pts	No. (%) Patients Fully Effective	Partially Effective	Ineff.	Not Evaluated
VF	60	36 (60)	15 (25)	7 (12)	2 (3)
VT-Sync	50	28 (56)	16 (32)	0 (0)	6 (12)
VT	81	48 (59)	25 (31)	5 (6)	3 (4)
VEB	1	1 (100)	0 (0)	0 (0)	0 (0)
SVA	49	40 (82)	8 (16)	0 (0)	1 (0)
Total	241	153 (63)	64 (27)	12 (5)	12 (5)

Twelve patients (5%) were not evaluated, generally because therapy was discontinued very early, before a valid assessment could be made Although 153 patients (63%) were fully responsive to amiodarone, and 64 (27%) had a partially effective rating, 26 of these 64 patients were treated with additional antiarrhythmic agents Twelve patients (5%) were unresponsive to amiodarone

Therefore, a total of 217 out of 241 patients (90%) were fully or partially responsive to amiodarone after lack of response, or intolerance, to prior antiarrnythmic therapy Of 192 patients treated for ventricular arrhythmias 169 (88%) achieved a fully or partially effective response

Some variation was noted in the different centers as shown in Table 31

TABLE 31 RESPONSE TO AMIODARONE ACCORDING TO INVESTIGATOR

Investigator	No (%) Patients Rated as Fully Responsive VF	VT	SVA
Fisner	3/7 (43)	11/33 (33)	--
Haffajee	8/14 (57)	12/18 (66)	14/18 (78)
Rakita	7/10 (70)	21/37 (56)	2/2 (100)
Singh	10/11 (91)	17/17 (100)	20/22 (91)
Zipes	8/18 (44)	16/26 (62)	4/6 (67)

A lower percentage of patients in Dr. Fisher's center were rated as fully responsive. Demographic data, described previously, showed this center to have a more seriously ill patient population, and had received the greatest number of prior antiarrhythmic trials (see Patient Description, Section B.1).

Among the 9 patients with Wolff Parkinson-White syndrome, amiodarone was fully effective in 6, partially effective in 1 and not rated in 2.

e. Results of Ventricular Arrhythmias Documented by Holter Recordings

Of the 241 patients treated with amiodarone, 202 had Holter recordings available for review, but only 114 had Holters both prior to and during amiodarone therapy. (In other cases, Holter recordings had been performed but copies of results were not available) Approximately 75% of the patients were taking one or more prior antiarrhythmic agents at the time of baseline monitoring Because patients had refractory, often life-threatening, arrhythmias that required urgent treatment, it was not always possible to obtain baseline 24-hour Holter recordings.

The subset of patients with baseline and treatment Holters might therefore, represent patients with more stable arrhythmias in which full baseline evaluations were feasible Overall efficacy assessment in all 241 patients and in the 114 patients with baseline and treatment Holters is shown in Table 32. The overall efficacy response in the 114 patients with Holters is similar to that in the entire study population.

TABLE 32 EFFICACY RESPONSE IN ALL PATIENTS VS PATIENTS WITH HOLTERS

	No. (%) Patients	
Response	Detailed Study (N=241)	Patients with Holter data (N=114)
Fully Effective	153 (63)	68 (60)
Partially Effective	64 (27)	36 (32)
Ineffective	12 (5)	5 (4)
Unknown	12 (5)	5 (4)

Holter results are shown in Table 33.

TABLE 33 ARRHYTHMIA COUNTS BY HOLTER RECORDS

Study Phase	VT beats/ hr	VT beats/ longest run	VT runs/ hr	Couplets/ hr	VEB/ hr
Baseline	453+450* (96)	3 1+0.9 (51)	11 1+5.9 (55)	7+3.5 (48)	289+46.5 (101)
Loading	0+0 0 (43)	1.3+0.7 (21)	0.4+0 2 (50)	2+0.7 (40)	91+35 1 (72)
Maintenance less than or equal to 3 mo	0+0 0 (31)	0 2+0 2 (21)	0 2+0 1 (44)	0+0 0 (35)	51+23 7 (55)
Maintenance greater than 3 mo	0+0 0 (25)	0 5+0 5 (20)	0 1+0 1 (37)	1+0 5 (30)	17+5 0 (48)

* Value excludes patients with no VT during all study phases and one patient with 150 VT beats/min

Number of patients listed in parentheses

Mean ± SEM

The post-treatment results show a substantial effect of amiodarone Amiodarone essentially eliminated VT, and the response obtained in the early maintenance phase (less than 3 months) was maintained during continued treatment

Ninety-six patients had quantitative VEB data on baseline and treatment Holters There was a 31% reduction from the baseline value (309 VEB/hr) during loading phase, and a 57% reduction in total VEB from the baseline value (259 VEB/hr) during maintenance phase A 95% or greater reduction in total VEB from baseline was seen in 26/70 (37%) patients during loading and 35/72 (49%) during maintenance treatment

Reduction in VT, after 6 to 14 days of loading therapy, preceded the reductions in couplets and VEB, which were not established until after more than 14 days of therapy The significance of this observation is uncertain, since the number of patients in whom VT was assessed is less than the number of patients with couplet or VEB data Rosenbaum et al (1983) had observed a progressive

response in patients with warning arrhythmias, suppression of VT occurred first, followed by suppression of couplets, total VEB and finally, multiform VEB The overall response to amiodarone was established in the late stage (greater than 14 days) of the loading phase. At that time, there was a 75% reduction from baseline in VT, a 67% reduction in VEB and a 71% reduction in couplets. Greater variability of response was seen during the early loading phase, including an overall mean increase in VEB in the first 7 days. The antiarrhythmic effect of amiodarone was well maintained with increasing duration of treatment although the number of patients with data beyond 15 months of treatment was small

f Deaths Among Patients Treated

Of the 241 patients treated with amiodarone there were 37 deaths reported Of these, 10 were due to cardiac arrhythmias, 5 due to CHF, 3 due to myocardial infarction, 3 due to pulmonary edema, 3 during postoperative procedures (post-cholecystectomy, postaneurysmectomy-coronary artery bypass, and postoperative ruptured abdominal aortic aneurysm), 2 reported as sudden deaths with no known cause, and 2 due to shock. Other causes of death included GI bleeding (1), renal failure (1), carcinoma (1), stroke (1), cerebral hemorrhage (1), subdural hematoma (1), terminal chronic obstructive pulmonary disease (1), and diabetic gangrene with sepsis (1) Finally, one patient who died 2 months after treatment was withdrawn because of early pulmonary fibrosis This patient complained of dyspnea prior to death Concerning the 10 deaths due to arrhythmias, 5 were listed as sudden death, VT in 2 (1 patient was treated for only 1 day), nonspecific ventricular arrhythmia in 1 and unknown arrhythmia in 2 Two of the 10 arrhythmia deaths occurred subsequent to amiodarone dose reduction

There were 3 additional deaths due to arrhythmia that occurred more than 1 week after amiodarone was discontinued (in 2 cases, discontinuation was inadvertent) Two of the 3 deaths were sudden and the third was noted as "probable arrhythmia".

This study was not designed to assess the effect of amiodarone on survival or reduction of arrhythmic deaths. Nevertheless, the incidence of fatal arrhythmias while on amiodarone (10/241, 4.1%) appears relatively low for this population Of the

10 arrhythmia deaths on amiodarone, therapy was rated by investigators as fully effective (prior to death) in 4, partially effective in 2, ineffective in 2 and was not listed in 2. The incidence of death due to arrhythmia was 4/153 (2.6%), 2/64 (3.1%), 2/12 (16.7%) and 2/12 (16.7%) in patients with full, partial, no or unknown responses, respectively, to therapy.

In patients with VF or VT/syncope who were fully responsive to therapy, one-year survival rates (Kaplan-Meier) in terms of total deaths and arrhythmia deaths were 0.92 and 1.00, respectively. Patients in this category with less than full effectiveness did less well. On the other hand, patients with VT/VEB who had a full response suffered a number of arrhythmic deaths. Actuarial survival rates according to arrhythmia and response are listed in Table 34.

TABLE 34 ACTUARIAL SURVIVAL RATES

Arrhythmia	Efficacy Response	Total (Arrhythmia) Survival Rates[@] 1-year	2-year	3-years
VF, VT/Sync	Full	50 (55)/55	25 (24)/25	6 (6)/6
	Other*	23 (32)/36	13 (13)/13	5 (6)/6
VT, VEB	Full	40 (41)/44	23 (24)/24	5 (7)/7
	Other*	22 (22)/23	9 (10)/10	4 (4)/4
SVA	Full	35 (36)/36	20 (21)/21	5 (5)/5
	Other*	7 (7)/7	4 (4)/4	3 (3)/3

[@]Numerator = number of survivors (survivors plus nonarrhythmic deaths) whereas denominator = number alive at the end of the interval plus number died during that interval

*Includes patients who were partially responsive, unresponsive and patients with no evaluation

[$]Excludes 2 patients who died after less than 7 days of therapy

The survival of amiodarone treated patients in this study and in most other reports (see section C 3 below, literature) compares favorably with historical controls, although available historical data are quite limited. Baum et a . (1974) provide the best available data on the untreated morbidity of patients resuscitated from out-of-hospital VF, finding mortality at two years of 14% and 47% in patients with and without, associated acute myocardial infarct on at the time of cardiac arrest, respectively. The striking difference in outcome

based on presence or absence of myocardial infarction should be emphasized. In addition, it should be noted that by no means did all patients with a documented cardiac arrest have a recurrence during one- to two-year period, so that failure to recur in a given patient is not evidence of drug effectiveness Only valid group comparisons can demonstrate effectiveness Richard et al. (1983) found that 38 of 165 stable patients 10 days post-myocardial infarction had VT inducible on electrophysiologic testing. During the following year, 8 of these 38 patients (21%) had sudden cardiac death This suggests that inducibility of VT carries a relatively poor prognosis and may allow comparison with similar groups treated with amiodarone. Individual patient subgroups may have a still worse prognosis Schulze et al (1977) found that postinfarction patients with complicated ventricular arrhythmias (Lown Class III-V) and poor cardiac function (LVEF less than 0 40) had a one-year mortality of 66% Obviously, it is very difficult to compare results in one uncontrolled series with another as the patient substrate is a critical determinant of outcome

5 Duration of Therapy and Amiodarone Dose

Among the 241 patients, the mean duration of loading and maintenance phases was 38 and 432 days, respectively

Duration of treatment at the time that amiodarone was discontinued or when the survey was completed (for patients continuing amiodarone) is listed in Table 35.

TABLE 35 DURATION OF AMIODARONE THERAPY AT FINAL DATA POINT

Study Phase	No Pts All Pts	Entering Phase VA	SVA
Loading Phase	241	192	49
Maint Phase (mo)			
less than or equal to 3	223	175	48
greater than 3 less than or equal to 6	198	157	41
greater than 6 less than or equal to 12	168	129	39
greater than 12 less than or equal to 18	115	84	31
greater than 18 less than or equal to 24	65	46	19
greater than 24	36	25	11

Of the 241 patients, 160 were still receiving amiodarone at the final data point, the remaining 81 patients included 47 who discontinued therapy and 34 who died. (Of the 81 patients, 17 had therapy discontinued or died during the loading phase and 64 during maintenance phases.) The mean duration of treatment of the 12 patients who were unresponsive to amiodarone was 56 days, 7 of the 12 received only loading treatment Obviously, that is a long time to await such an evaluation in people with life-threatening arrhythmias. Once patients were established on therapy that was considered effective, they did reasonably well

Some investigators have emphasized the observation that nonresponders are detected relatively early Whether this is meaningful or gives guidance to therapy is difficult to determine, it may merely reflect the tautology that patients who are still at high risk after therapy (nonresponders) tend to die and those who are not at risk do well. It could suggest that amiodarone is not fully effective in the first month or so of therapy, but this cannot be proved Morady et al (1983) reported that 14 of 17 failures (recurrence of VT or sudden death) occurred within 4 months of initiating therapy Patients with and without recurrences were similar except for a significantly lower ejection fraction (less than or equal to 25%) in those with recurrence Cameron et al (1982) treated 25 survivors of VF for 22 2 (12-33) months Of a total of 10 deaths probably due to arrhythmia, 6 occurred within the first month of therapy and only 2 occurred after 3 months

Kaski et al (1981) treated 23 patients with sustained, recurrent, symptomatic VT. Five patients had arrhythmic deaths, 2 of 5 died within 45 days and were considered absolute nonresponders Clinical features suggesting poor prognosis (short- and long-term) included refractoriness to lidocaine, requirement for repeated cardioversion, low-output heart failure and large ventricular aneurysm. The apparent non-responder to amiodarone thus remains at high risk and must be considered a candidate for alternative therapy (added drug, surgery, or implanted defibrillator, for example) Survival in those considered responders seems reasonably good (but see literature discussion below for methods of response assessment)

The mean initial loading doses and the initial, final and overall maintenance doses used in the Detailed Study are summarized in Table 36

TABLE 3b AMIODARONE DOSE

Arrhythmia	Mean + SEM TDD (mg/day) Initial Loading	Initial Maint	Final Maint	Overall Maint
Ventricular	1079 + 43 9 (192)	597 + 25 1 (175)	447 + 22.3 (174)	484 9 (175)
Supraventricular	1091 + 69 7 (49)	500 + 27 8 (48)	384 + 39 1 (43)	404 0 (48)
All Patients	1081 + 37 7 (241)	576 + 20 7 (223)	434 + 19.4 (222)	466 8 (223)

TDD = total daily dose
(Number of patients)

In the Detailed Study, approximately one-half of the patients treated for ventricular arrhythmias continued their prior antiarrhythmic therapy for a mean of 16 8 days during amiodarone loading (Combination antiarrhythmic therapy must be used cautiously, however, as described in Section V C.)

Pharmacokinetic projections using a 3-compartment model have predicted that the amount of amiodarone present in the "effect" compartment might drop below a minimum effective level if too abrupt or premature a change is made from loading to maintenance doses (Siddoway et al , 1983) Therefore, empirical dosage regimens have incorporated a stepwise reduction from loading to maintenance doses Following a loading regimen of 600 to 1200 mg/day (occasionally higher) administered for several weeks, an intermediate phase (maximum dose 800 mg/day) lasting 1 month would permit gradual reequilibration Specific doses and durations of the loading and intermediate phases must be individualized, in view of the variable time required to reach steady state In a patient showing some, but incomplete response, progressive increases in loading doses (especially if doses less than or equal to 600 mg/day were used) or prolongation of the loading phase might be beneficial Doses above 2000 mg/day are not likely to achieve additional response, and frequent, reversible neurologic and gastrointestinal symptoms are more likely to accompany such high doses

During maintenance treatment, the mean final dose among the 64 patients who discontinued amiodarone or died was higher (605 + 36 4 mg/day) than among the 158 patients who were still continuing amiodarone at the final data point (364 + 11 1 mg/day) This is not surprising, poor responders would be expected to have dose increased in an

attempt to elicit a response Patients who discontinued treatment because of ADRs may also be expected to have been receiving higher doses

Initial loading doses were comparable in the supraventricular and ventricular arrhythmia groups, although the latter patients had a smaller reduction in dose from the initial to the final maintenance levels The progressive dose reduction over time is shown in Table 37

TABLE 37 AMIODARONE DOSE ACCORDING TO DURATION OF THERAPY

	All Patients		Ventricular Arr		SVA	
Study Phase*	No Pts	TDD (mg/d)	No Pts	TDD (mg/d)	No Pts.	TDD (mg/d)
Load 1-7 Days	239	1015 ± 26 7	190	1012 ± 28 9	49	1029 ± 67 3
Load 8-14 Days	209	893 ± 25 7	167	889 ± 27 0	42	912 ± 70 0
Load 14-28 Days	182	811 ± 23 5	143	814 ± 25 3	39	802 ± 58 8
Maint less than or equal to 3 mo	223	544 ± 17 4	175	560 ± 20 9	48	485 ± 25 0
Maint greater than 3 less than or equal to 6 mo	198	463 ± 13 3	158	477 ± 15 8	40	407 ± 19 8
Maint greater than 6 less than or equal to 9 mo	169	413 ± 13 0	130	425 ± 14 8	39	376 ± 26 5
Maint greater than 9 less than or equal to 12 mo	150	368 ± 11 0	113	384 ± 13 8	37	321 ± 19 1
Maint greater than 12 less than or equal to 15 mo	115	347 ± 12 7	84	366 ± 15 4	31	322 ± 21 2
Maint greater than 15 less than or equal to 18 mo	85	343 ± 15 6	62	349 ± 19 0	23	330 ± 29 9
Maint greater than 18 less than or equal to 21 mo	66	350 ± 19 1	47	364 ± 23 3	19	316 ± 32 3
Maint greater than 21 less than or equal to 24 mo	50	327 ± 20 6	38	337 ± 23 8	12	290 ± 41 4
Maint greater than 2 yrs	36	316 ± 23 0	25	326 ± 27 7	11	294 ± 42 7

* Dose is calculated for each interval, using data from patients who continued therapy

TDD = total daily dose, mean ± SEM

SVA = supraventricular arrhythmia

The mean maintenance dose and duration of treatment, by arrhythmia and response, are presented in Table 38 (Data are not listed for 12 patients who did not have an efficacy evaluation)

TABLE 38 MEAN MAINTENANCE DOSE AND DURATION OF THERAPY ACCORDING TO RESPONSE

	Fully Effective			Partially Effective			Ineffective		
Primary Arr	No Pts	TDD (mg/day)	Dur Rx (days)	No Pts	TDD (mg/day)	Dur Rx (days)	No. Pts	TDD (mg/day)	Dur Rx (days)
VF	36	444	497	15	647	476	7	600	46
VT/Sync	28	507	399	13	579	452	0	-	-
VT	48	400	496	25	482	409	5	447	69
VEB	1	400	83	0	-	-	0	-	-
SVA	40	372	545	8	549	626	0	-	-

TDD = total daily dose

For all arrhythmias, the dose was lowest in patients who were fully responsive to therapy. The doses listed in Table 39 are mean maintenance doses, final maintenance doses were slightly lower. In patients judged fully responsive to amiodarone, final maintenance doses were 393 + 14 7 mg/day (N=109) and 340 + 26 9 mg/day (N=39) for ventricular and supraventricular arrhythmias, respectively

A higher dose was required in patients with ventricular arrhythmias compared to patients with supraventricular arrhythmias This may be due to differences in the mechanism of the underlying arrhythmia and to patient characteristics, those treated for supraventricular arrhythmia were less likely to have a history of congestive heart failure, ischemic heart disease, cardiomegaly, cardiomyopathy and reduced left ventricular ejection fraction The literature also has consistently reported a need for higher maintenance doses in patients with life-threatening ventricular arrhythmias than patients with supraventricular arrhythmias

Differences were observed between the doses used by the 5 investigators as shown in Table 39

TABLE 39 AMIODARONE DOSE ACCORDING TO INVESTIGATOR

	Fisher N=41	Haffajee N=50	Rakita N=50	Singh N=50	Zipes N=50
Mean TDD (mg/d)					
Loading (initial)	926	1122	1497	1452	800
Loading (intermed)	640	927	430	1028	702
Maintenance	595	356	460	462	427
Duration Rx (days)					
Loading	62	36	30	34	30
Maintenance	310	676	390	405	319

TDD = total daily dose

It is likely that some differences were related to patient characteristics (Dr. Fisher's patients more frequently had severe underlying cardiovascular disease) and to the individual investigator's dosage regimens (refer to Sections VI B 1 and VI B 2 Patient Description and Study Methodology)

- Determination of the Optimal Amiodarone Dosage

Because of the study "design" (Section VI B 2) it is not possible to define a minimum effective dose from Ives data Furthermore, in patients with symptomatic, life-threatening ventricular arrhythmias, it is difficult to precisely define a minimum effective dose for any antiarrhythmic agent Nevertheless, some conclusions can be made concerning effective antiarrhythmic doses from the Detailed Study and the literature In Section VII, it will be shown that these doses are also reasonably safe and well tolerated, considering the intended patient populuation

Data from the 112 patients with reduction in amiodarone maintenance dose (Section VI B 4) suggest that total daily doses of 200 to 400 mg are required in the treatment of most ventricular arrhythmias, but that some patients who are controlled on 400 mg per day cannot be controlled on lower doses, these patients, who relapsed when amiodarone dose was reduced from 400 to 200 mg pe day, showed restoration of arrhythmia control when the dose was increased again to 400 mg Occasional patients, however, appear to require 600 mg per day Only limited conclusions can be drawn from the dose reduction study because there was no consistent schedule for detitration and patients did not have uniform loading and maintenance dosages prior to dose reduction

The Collaborative Group for Amiodarone Evaluation (1984) carried out systematic dose reduction When response of Lown arrhythmia classes 3 and 4 was assessed after 1 month of treatment, 35 patients responded (reduction in VEB, couplets and triplets of at least 83%, 75% and 85%, respectively) to a daily dose of 400 mg per day (serum amiodarone level 0 80±0 38 mg/l) One month after reduction of amiodarone dose to 200 mg/day, 24 patients continued to respond (serum amiodarone concentration 0 67±0 31 mg/l), 10 became nonresponders (serum amiodarone concentration 0.68±0 47 mg l), and 1 patient died of ventricular fibrillation One month after the dose of the 10 nonresponders was increased to 400 mg per day, arrhythmia control was restored in all 10 patients (amiodarone concentration 0 97±0.62 mg/day). This study shows an antiarrhythmic effect at doses of 200 to 400 mg per day, but also shows that there are responders to 400 mg who are not adequately controlled on lower doses.

The maintenance doses established empirically in the literature reflect an effort to control the arrhythmia with minimal adverse effects This is illustrated by the experience of Greene et al. (1983) who treated 70 patients with symptomatic, refractory arrhytnmias (66 with VA and 4 with SVA) with a 1-week loading dose of 1200 mg/day and 600 mg/day maintenance. Because of a high incidence (93%) of adverse effects at this dose level, dose reductions were often necessary, the mean dose fell from 572 ± 283 at 45 days to 372 ± 174 mg/day after 6 months At the end of 6 months 42 (60%) of the patients required daily dosage reduction due to side effects Also, at the end of 6 months 8 patients discontinued treatment because of noncardiac side effects

Westveer et al (1984), using maintenance doses of 400 (N=30) and 800 mg/day (N-49), found that 45% of patients on the higher dose required detitration for adverse effects, in comparison to 7% of patients on 400 mg/day, but saw no difference in effectiveness by life table analysis

In a U K survey by Harris et al (1983) of 140 patients, 600-1200 mg/day was administered for 1 week as a loading dose, followed by 400-600 mg/day for 1 month, thereafter the dose was titrated according to the individual patient's response Only 11 patients required maintenance doses of 600 mg/day or more Higher doses were required in 46 patients with VT (440 mg/day) and complex VEB (400 mg/day) than in supraventricular arrhythmias (310 mg/day in 15 patients with chronic atrial fibrillation and/or flutter, 280 mg/day in 38 patients with paroxysmal atrial tachycardia and 350 mg/day in patients with WPW and SVA)

C Supportive Efficacy Data

1 Global Survey

The efficacy of amiodarone was also tabulated from the Global Survey, although this study was intended primarily to evaluate safety in a large number of patients and included only patients who had died or stopped amiodarone because of an adverse effect. Nevertheless, an efficacy evaluation (without supporting documentation) was available for 598 of the 1024 patients Efficacy criteria were similar to the definitions listed for the detailed study in Section VI B 3 Among 598 patients, amiodarone was considered fully effective in 290 (49%), partially effective in 180 (18%) and ineffective in 128 (34%) (Efficacy was not listed according to type of arrhythmia) Compared with the Detailed Study, the percentage of fully responsive patients was lower (49% vs 63%) and the percentage of nonresponders was higher (34% vs 5%) This difference might reflect differences in patient populations, because, as noted, only patients who died or discontinued amiodarone because of ADR were included in the Global Survey Mean loading and maintenance doses in the Global Survey were 918 and 528 mg/day, respectively, mean duration of loading and maintenance phases were 39 and 156 days, respectively (Dose information was available in only approximately 50% of patients) Total duration of therapy was 171 days

2 Additional Clinical Experience (Dr D Zipes)

The responses of 230 patients with refractory VF (64), sustained VT (114), or nonsustained VT (52), and 74 patients with SVA (reported in part by Heger et al, 1983) treated by Dr Zipes are presented in Appendix II Those patients treated for ventricular arrhythmia had received a mean of 4 drugs prior to amiodarone, and had severe underlying cardiovascular disease with a mean left ventricular ejection fraction of 0 33, 69 of 230 patients were in NYHA functional Class III or IV The full details of treatment and results can be seen in Appendix II Of special interest is the large series of patients subjected to electrophysiologic (EP) testing Among 129 patients undergoing electrophysiologic study (EPS) who had inducible VT and who continued amiodarone, 110 still had inducible VT during amiodarone treatment and 19 were no longer inducible after amiodarone During follow-up none of the 19 noninducible patients had recurrent VT or death In contrast 25/108 (two discontinued) of the inducible patients experienced

recurrence of VT during a follow-up of 11±2 months This 23% recurrence rate is probably better than the rate would have been without treatment (all patients had had observed recurrences on several prior drugs) but does not appear to be as satisfactory as the rate for the suppressed patients Of course, the two groups may not have been comparable and were "outcome defined" subgroups

3 Literature

There is a large and growing body of literature reporting on the results of treatment of refractory, life-threatening ventricular arrhythmias with amiodarone It is, unfortunately, very difficult to compare the patient populations in different trials or to compare treated patients with a valid historical control Dosing regimens have been developed empirically and have been highly variable, and the basis for deciding to continue amiodarone or to alter the dose have varied from study to study The literature does, however, offer some guidance as to outcome, dose selection, and monitoring of treatment effects It should be noted that in most series, survival or effectiveness is reported in patients who are placed chronically on the drug, those with no initial effect or intolerance are not included The series, in other words, are not reported as "intention-to-treat" in most cases

Most of the studies have involved patients considered at high risk of death because of a history of VT/VF or resuscitation, and controlled comparison with no treatment has been out of the question Even comparison with alternative agents is difficult, as amiodarone has been considered a "last resort agent " The only available comparisons are those with expected mortality based on historical series

Survival in series of amiodarone-treated patients has been reported by many investigators Cameron et al (1982) reported 10 deaths in a group of 25 survivors of VF who were followed for 22 2 months (12-33) on amiodarone Among the 10 deaths in this study, 6 were due to documented VF, 2 were sudden deaths and 2 were not documented Only 1 of 16 patients rated as fully responsive at 3 months (no recurrence of VT or VF up to that time) subsequently died In contrast, all patients with a reduction, but persistence of symptomatic VT (3) or no improvement (6) after 3 months of amiodarone subsequently died of known or probable arrhythmias In this case the persistence of nonfatal VT presaged an ultimately fatal outcome while elimination of spontaneous VT was associated with a good outcome

Peter et al (1984) treated 33 consecutive survivors of cardiac arrest from ventricular arrhythmias, not associated with a new acute myocardial infarction (AMI), with amiodarone for a median of 24 months. There were 5 sudden cardiac deaths (15%). The same group (Peter et al, 1983) had earlier reported an arrhythmic mortality of 10/77 among patients with a history of sustained VT including some with episodes of sudden death, following a mean of 20.0 months. In that study, therapy was assessed by symptoms and ambulatory ECG recordings.

Morady et al (1983a) used electrophysiologic testing to guide therapy in 45 survivors of cardiac arrest. Eleven patients had no inducible VT and, with therapy directed at their underlying heart disease (and empiric antiarrhythmic therapy in 2 patients), there were no recurrences of symptomatic VT or cardiac arrest during a mean follow-up of 19 months. The remaining 34 patients had inducible VT. In 9 of these 34, conventional antiarrhythmic therapy suppressed induction of VT, after a mean follow-up of 20 months, 3 of the 9 (33%) had recurrent VT or sudden death. In 25 of 34 patients, induction of VT could not be suppressed by conventional drugs, 23 were treated with amiodarone and over 18 months, 2 had recurrent VT or sudden death and 21 (91%) did not. Inasmuch as these investigators (Morady et al, 1981) and others (Heger et al, 1981, Hamer et al., 1981) observed that induction of VT during chronic oral amiodarone therapy did not preclude a good clinical response, the 23 patients on amiodarone did not undergo further electrophysiological testing.

Fogoros et al (1983) reported on their treatment of 77 patients with recurrent VT or VF and, unlike many series, included all patients exposed to amiodarone, including early failures. Intolerable side effects were counted as drug failures. Excluding 7 early dropouts (4 deaths during first week and 3 dropped because of inducible VT on programmed electrical stimulation (PES) during the first month, the actuarial incidence of drug efficacy at 12 months was 52% and at 24 months 28%. In all, 32 patients were successfully treated and 38 failed to respond or had to be dropped. Fourteen of the 38 failures occurred within a month. If only patients on treatment at least a month are considered, the success rate at one year was about 70% and at 2 years about 35%. Failure was based on severe side effects (14), sudden death (5), symptomatic recurrence of VT (15), or recurrent asymptomatic NSVT (1). If the 14 discontinuations due to side effects are not included, the SD or recurrent VT/VF occurred in 24/56 or 42% of all patients, and mortality was 8/56 or 14%, not too different from other series. Among the 47 patients treated at least one month who did not stop drug

because of side effects, 15/47 (32%) had late failure It is this figure that is probably most comparable to those for other series, which tend not to count side-effect dropouts as efficacy failures and do not count initial failure as part of the treated group Again, without an adequate control group, it is difficult to evalute the success of the drug, but the untreated annual mortality of such a population is almost surely higher than 15%

A variety of means have been used to monitor the effectiveness of amiodarone and predict long-term success just as with other drugs, including measuring effects on Holter VPB rates, frequency of NSVT or VT episodes on Holter and suppression of PES inducibility of VT/VF There is substantial controversy regarding the best method of predicting outcome, and particularly on the role of programmed electrical stimulation While for most agents, suppression of PES inducibility has correlated well with survival and suppression of episodes of sustained VT/VF, an impression has existed that amiodarone use can lead to a good outcome even without suppression The following data are relevant to the question

Greene et al (1983) found that in 70 patients with VT/VF, total VEB count on Holter monitoring was not predictive of long-term response (recurrence of VF or sustained VT) There was a weak trend suggesting patients with high density VEB at baseline who had a marked reduction on amiodarone did better than patients with fewer VEB at baseline and increased VEB on amiodarone Because of considerable overlap of Holter responses in patients with and without later recurrences, Greene and associates did not find Holters to be predictive of overall response (arrhythmia recurrence)

In contrast, Kennedy et al (1984) found that treatment failure (recurrence of VT or sudden death) in 6 of 24 patients treated with amiodarone (doses 200 to 800 mg/day for greater than or equal to 4 weeks) was predicted best by a combination of greater than or equal to 1 VEB/1000 normal beats and inducible sustained VT on programmed electrical stimulation during treatment (The combination of findings was more accurate than each individual finding) Low VEB count on Holter (less than or equal to 1/1000 normal beats) was the best predictor of long-term success Results are shown in Table 10 In this study, very few patients became noninducible so the usefulness of that observation could not have been great, it appeared, however, that in inducible patients, the VEB rate did help predict outcome

TABLE 40 PREDICTION OF SUCCESSFUL RESPONSE (KENNEDY et al., 1984)

	VEB less than or equal 1*	VEB less than 1	SVT	VEB greater than 1 + SVT*
Success	13/14 (93%)	5/10 (50%)	7/12 (58%)	1/5 (20%)
Failure	1/14 (7%)	5/10 (50%)	5/12 (42%)	4/5 (80%)

*p less than 0 05 (success vs failure)
SVT = inducible sustained VT

In a study of 51 patients with sustained VT or VF, Waxman and coworkers (1982) found that amiodarone completely or partially abolished arrhythmia in 23 and 13 patients, respectively Nevertheless, only 5 of 43 patients were no longer inducible after amiodarone loading, prolonged therapy did not improve EPS results EPS does not appear to predict all of the patients who seem to do well It is important, however, to distinguish "doing well," as assessed by initial response, and long-term success

Hamer, et al (1981) reported experience similar to Waxman's In 9 patients with sustained VT/VF (6) or NSVT (3) given amiodarone over a period of 10-24 months, VT was prevented in 5 patients with frequent VT prior to treatment, NSVT was abolished in 3 patients, and VF was prevented in a patient with a putative 30% annual risk Nonetheless, sustained VT inducible by PES at baseline in 7 remained inducible in all

Zipes, as noted above, found that suppression of inducibility was associated with a very good prognosis (19/19 did well) but that 75% (83/110) of patients still inducible also did well, without recurrence of VT Zipes and coworkers (Klein, 1985) have been seeking to develop a discriminant function to predict which patients who were still inducible on amiodarone were at greatest risk They found, in work thus far reported only as an abstract, that easier inducibility (fewer extrastimuli) had been seen in 11/16 (69%) of patients with recurrent sustained VT or VF vs 13/69 (19%) of asymptomatic patients Patients requiring more aggressive stimuli did well, with 2/16 (13%) recurring Moreover, recurrent VF was seen only in patients with easier induction or VT cycle length at induction of less than or equal to 370 msec

Others have sought predictors of success other than, or in addition to, PES evaluation Veltri et al (1985) studied 13 patients for a mean follow-up of 24 months with recurrent sustained VT including 9 with SD syndrome

3 with syncope and one with presyncope, 11 had sustained VT at control PES, while 2 had only NSVT Late PES (at least 6 weeks, because of reports of lack of early effect) showed loss of inducibility in only one patient, and one patient with inducible NSVT developed SVT after amiodarone Despite the poor PES response, 8/13 patients were free of clinical arrhythmic events Of the 5 who did have events, two were patients without sustained VT There was no apparent consistent change in ease of induction The authors suggested that the patients remained vulnerable to sustained VT but that triggers to such arrhythmics were reduced

The same authors have recently reported in an abstract (Veltri, 1985a) that in 52 amiodarone-treated patients with sustained VT who also had NSVT on baseline Holter, response of NSVT after 1 week of loading (1200 mg/day) amiodarone therapy predicted outcome Thirty-four patients had suppression of NSVT, 18 had continued NSVT At a mean follow-up of 8 months only 3 (9%) of suppressed patients had recurrent VT or SD, compared with 10 (56%) of the patients with continued NSVT

Many authors have found PES highly predictive of outcome McGovern et al treated 18 patients with recurrent symptomatic VT or VF, who had failed a mean of 8 5 drugs and who had symptoms for one to four years, with amiodarone at a loading dose of 600-1200 mg/day and maintenance doses of 200-1000 mg/day All patients had inducible VT prior to treatment After a mean of 12 days (range 8-42) of treatment, 5 patients were not inducible, and added mexilitine rendered two more not inducible A partial response (more difficult inducted) was seen in 2 other patients In the 9 remaining, amiodarone had no effect on response to stimulation or made it easier to induce Among the full or partial responders, after a mean of 22 3 months (range 7-42 months), there were no symptomatic arrhythmias In the nonsuppressed group there were 2 sudden deaths (2 months and 20 months) and 3 with recurrent VT, at 4 days, 4 weeks and 6 weeks In all 3 cases, patients developed "incessant VT" requiring multiple cardioversions not responsive to previously effective parenteral medications In a later publication, reporting on 30 patients (including the above 18) McGovern (1983) found that a group of 16 patients in whom amiodarone suppressed induction or increased the difficulty of induction had done well after a mean follow-up of 10 3 months, only one patient died, and that patient died at 27 months following dose reduction because of toxicity In contrast, 8 of the 14 whose arrhythmias were not suppressed had recurrent VT (6) or died

Horowitz et al (1985) have reported similar results in 100 consecutive patients with symptomatic VT/VF treated with amiodarone All patients had inducible sustained VT/VF before amiodarone therapy, but with loading dose treatment (oral loading dose of 1000 mg/day for 1 week and 800 mg/day for the second week or oral plus i.v loading of 600 mg oral plus 10 mg/kg/24 hours i v. for 3 days following by 800 mg/day for 7 days), PES at day 9, 10, or 11 some showed changes in inducibility Twenty patients became noninducible either with amiodarone alone (18) or with amiodarone plus procainamide (2) Over a mean follow-up of 18 months (range 4-31, all at least 12 months except for one patient who died of AMI at 4 months) there were no instances of recurrent VT/VF or sudden death Two patients died of nonarrhythmic cardiac causes and 3 patients stopped treatment because of side effects

Eighty patients remained inducible with sustained VT in 76, VF in 2 and NSVT in 2 Amiodarone was used alone in 69 and in combination with procainamide in 7 and quinidine in 4 Over a mean follow-up period of 12 months (range 2-32) symptomatic VT/VF recurred in 38/80 (48%) There were 7 nonarrhythmic cardiac deaths and 6 patients had amiodarone discontinued because of toxicity Recurrent VT/VF recurred between 1 and 3 months in 20 patients and between 3 and 18 months in 18 doses at recurrence were 600 mg/day in 21, 400 mg/day in 14 and less than 400 mg/day in 3

The recurrence rates were highly significantly different for the two groups, but there were no differences in baseline arrhythmia, ejection fraction (24-25% for both groups), age, or severity of heart disease Mean amiodarone plasma levels were lower in the noninducible group at time of PES (1 4 vs 1 7 mg/l) and during chronic treatment (1 8 vs 2 1 mg/l) as was mean maintenance dose (391 vs 432 mg/day) and QTc interval (462 vs 471 msec) although these differences were not significant

The inducible patients were examined further for predictors of recurrence and survival There were no significant differences in plasma concentration or QTc, but amiodarone dose was significantly lower in the recurrence-free group (391 vs 499 mg/day) and the plasma concentration was somewhat lower in that group (1 9 vs 2 2 mg/l) There was, however, a highly significant difference in ability to tolerate the induced arrhythmia that correlated strongly with survival Among 56 patients with inducible VT who did not develop severe symptoms at induction, 26 (46%) ad recurrent VT but all survived Among 24 who developed severe symptoms

(cardiovascular collapse or angina and near syncope), 12 (50%) died suddenly, accounting for all of the apparent arrhythmic fatalities in the study VT cycle lengths were significantly shorter in the patients with severe symptoms during induced VT (304, range 250-320, vs 411, range 300-580 msec)

The study suggests, like the work of McGovern and Zipes, that noninducibility after PES carries a highly favorable prognosis To possible predictors of a good outcome in the inducible patients (along with very low VPB rates [Kennedy], more difficult inducibility [Zipes], and elimination of NSVT [Veltri]) can be added good tolerance of the induced arrhtnymia, which also correlates with relatively slow VT

In an abstract, Borggrefe et al (1983) reported similar results, finding recurrence in 8 (2 fatal) of 23 patients (34%) whose inducibility did not change from baseline, but no recurrence over a mean 11-month follow-up in patients who became noninducible (8) or more difficult to induce (5)

Lavery et al (1985), also in an abstract, reported results in 48 patients with refractory VT and organic heart disease After 4-6 weeks of an average dose of 715 mg/day, 24/48 were no longer inducible, while 24 were inducible, showing either the same VT as identified clinically (13) or a new morphology (11) The noninducible group after an unstated follow-up period had only 1/24 (4%) recurrence The inducible group had a recurrence rate of 8/24 (33%) Serum levels were similar in the two groups

It seems clear that amiodarone is fairly often successful in suppressing inducibility or making induction more difficult in highly refractory patients (Zipes greater than 19/129=greater than 15% [Zipes results are given as greater than 19 because he did not include patients whose induction became more difficult, who also do well], McGovern 9/18 - 16/30, 50 or 53%, Horowitz 20/100=20%, Lavery 24/48=50%, Borggrefe 13/36=36%) with the variability no doubt depending on technical details of the stimulus regimen and patient characteristics such as underlying heart disease, number of prior failures, and the particular arrhythmias The suppressed patients appear to do very well, with very low (less than 5%) recurrence rates

Patients not suppressed have not done as well, with recurrence rates of 30 to more than 50% But even in these patients mortality was not high, in the range of 15% in McGovern's and Horowitz's experience Horowitz found that good tolerability of the induced arrhythmia predicted survival of patients with recurrent VT

Some (Veltri, Hamer, Waxman) found low rates of suppression of induced arrhythmia but reasonably good outcomes nonetheless Predictors of a good outcome have been suggested, including low VPB rates (Kennedy) or complete suppression on Holter of NSVT (Veltri)

Little information exists concerning prospective evaluations of amiodarone against other antiarrhythmic agents Hoffman (1984) treated 50 consecutive patients with coronary artery disease and frequent (greater than 30/hr), high-grade (greater than or equal to Lown grade III) ventricular arrhythmias Drugs were evaluated after 2 to 6 weeks, with serum level monitoring in many patients First-choice drugs were quinidine (slow-release 750-1500 mg/day), mexiletene (600-800 mg/day) or a beta-blocking agent (sotalol, 320 mg or oxprenolol, 160 mg daily) Second-choice drugs were amiodarone (200-400 mg/day), prajmalium bitartrate (40-60 mg/day), disopyramide (400-450 mg/day) and phenytoin (200-300 mg/day) Treatment was considered effective when all repetitive ventricular ectopy (Lown grade IVa) was eliminated and when frequent multiform VEB were reduced to less than 30/hr according to Holter recordings There were 89 single drug trials The proportion of successful to total drug trials was 13/27 (48%) on amiodarone, 4/27 (15%) on quinidine, 7/26 (27%) on mexiletene, 3/11 (27%) on beta blockers, 1/8 (13%) on prajmalium bitartrate and 1/5 (20%) each on disopyramide and miscellaneous drugs

In addition, there were 15 trials using amiodarone in combination with mexiletene (7), quinidine (4) or other agents (4), 9 of 15 trials (60%) were successful This study suggests a higher response rate on amiodarone despite its use as a "second-line" therapy

In a another study Schmidt (1984) studied 34 patients with Lown grade IV arrhythmias on baseline Holter recordings Therapeutic efficacy was defined as a 90% reduction of couplets and a 100% reduction of salvos, according to Holter recordings at week 1 and months 1 and 3 Class I antiarrhythmic drugs (TDD) used were disopyramide (600-900 mg), flecainide (200-300 mg), mexiletene (600-800 mg), prajmalium (60-80 mg), propafenone (600-900 mg) and tocainide (1200-1800 mg) If Class I drugs were not effective initially or during follow-up, amiodarone therapy was initiated One or more Class I antiarrhythmic agents were effective acutely in 78% of patients, however, efficacy decreased to 56%, 28% and 15% after 1 week and 1 and 3 months, respectively The efficacy of amiodarone was 45% after 1 month and increased to 72% after 3 months

D Conclusions

Amiodarone is an effective antiarrhythmic agent In 241 patients previously unresponsive to or intolerant of other antiarrhythmic drugs, 59% and 82% of patients with ventricular arrhythmias (VA) and supraventricular arrhythmias (SVA), respectively, were described as having had a full response (elimination of VF, VT and complex VEB and/or 95% reduction of total VEB or complete elimination of symptoms associated with SVA), an additional 29% of patients with VA and 16% with SVA had a partial response to therapy. Therefore, of 192 patients treated for ventricular arrhythmias, 169 (88%) achieved a fully or partially effective response Of 49 patients treated for supraventricular arrhythmias, 48 (98%) were fully or partially responsive to amiodarone

According to Holter monitoring, during amiodarone maintenance therapy, VT was essentially eliminated and couplets and total VEB reduced from baseline by 50 to 73% (couplets), and 60 to 70% (total VEB) Among 24 patients who temporarily discontinued therapy, arrhythmia recurred in a high proportion (79%), control was reestablished after resuming therapy Eighty patients with syncope had no recurrence during amiodarone treatment (mean 434 days) The one-year survival rate in patients treated for VF or VT with syncope who were fully responsive to amiodarone was 100% In the group of 241 patients, the mean durations of loading and maintenance treatment were 38 and 432 days, respectively Mean loading doses of 1079 to 1091 mg/day were used, followed by gradual dose reduction to mean doses of 393 and 340 mg/day in fully responsive patients with VA and SVA, respectively

The literature supports effectiveness of amiodarone as measured by elimination of Holter evidence of VT, by suppression of PES-induced VT/VF and by good survival/recurrence experience, especially in patients with suppression of PES-inducibility

VII CLINICAL EXPERIENCE SAFETY

A Introduction

Several sources served as the database to evaluate the safety of amiodarone in the treatment of cardiac arrhythmias, and are summarized below

1 The Global Survey evaluated safety of chronic amiodarone treatment One hundred ninety-four of 242 (80%) IND holders (as of September 1982) responded to the survey Of the 4802 patients treated with amiodarone, specific details were furnished on 1024 patients who discontinued

therapy due to adverse reaction (N=399, 8%) or died during amiodarone treatment (N=625, 13%) Therefore, data from this survey provide information on a large number of patients who possibly presented the most negative safety profile Relevant clinical information, including adverse reactions (ADR), laboratory tests, chest X-rays, drug interactions, and effects of dose reduction and temporary discontinuation of the therapy (rechallenge) was collected As this survey did not provide information on the incidence of side effects in the total of 4802 patients, conclusions regarding only those patients whose treatment was terminated due to side effects and overall incidence of deaths during amiodarone therapy were made

2 In addition a Detailed Study of safety and efficacy was based on clinical data collected retrospectively from 5 major U S medical centers Amiodarone was given to patients with serious, life-threatening cardiac arrhythmias who had not responded satisfactorily to prior therapy or had not tolerated other antiarrhythmic agents Clinical details were collected on 241 patients treated with amiodarone in 5 major U S medical centers (Each of 4 centers provided data on 50 consecutive patients and one center provided data on all 41 patients treated) Information on all aspects of safety, i e incidence of all side effects (requiring or not requiring patient withdrawal from treatment), laboratory test results, chest X-ray evaluations, drug interactions, dosage reduction and rechallenge were evaluated Since the 241 patients of the Detailed Study were included among the 4802 patients of the Global Survey, the number of patients withdrawn from treatment and those who died are overlapping

A third source of ADR information is the reports of individual investigators who summarized their own experience, or, in one case, sought to bring together results from a group of investigators who were surveyed with a questionnaire and who responded with reports of experience in more than 1000 patients, many treated for more than a year This survey has been described briefly in an abstract (Mason, 1985) and at the November 1985 American Heart Association meetings and in a more detailed preliminary report to the FDA Although the underlying data (individual survey reports) have not been reviewed by the Agency, the quality and experience of the investigators, and the fact that a similar but less detailed survey was the basis for the Ives Global Survey demands that the results be given consideration A

limitation, however, is the fact that validation and complete analysis have not yet been accomplished On the whole, perhaps because of a longer mean follow-up, adverse reaction rates in the Mason review are somewhat more frequent than in the Ives Detailed Study or in most published reports Of particular concern is a 13% rate of pulmonary complications and, in general, a high dropout rate (16%) for ADR, although the latter is not higher than that in some published series such as Fogoros (1983), Heger (1983) and McGovern (1983)

The 8 centers, their principal investigators, and the numbers of patients surveyed were

Institution	n	Investigator
University of Utah	81	Mason, JW
Columbia University	84	Bigger, JT
Likoff Institute/Hanneman	226	Horowitz, LN
Massachusetts General Hospital	229	Ruskin, JN
San Pedro Peninsula Hospital	129	Cannon, DS
Stanford University/Sequoia Hosp	263	Winkle RA/Swerdlow, CD
Vanderbilt University	64	Woosley, RL
Washington University	235	Greene, HL

In general, this IND survey was consistent with the two Ives reports

This discussion of the safety experience with amiodarone addresses the following

Adverse Reactions

- Overview of ADR
- Terminations for ADR
- Dose and time relationship of ADR
- Response of ADR to dose reduction or temporary discontinuation

Laboratory Tests
Deaths

It should be appreciated that at least some amiodarone ADR occur only after a period of time, so that the rate of ADR should be based on the population actually at risk The overall rates using a denominator of all patients entered will underestimate the rate of such time related events, and will do so in proportion to the frequency of early drop-outs due to ineffectiveness, death, or acute ADR The discussions below will attempt to reflect the rate in long-term use to the extent possible

For overall comparative purposes, Table 41 summarizes results of the Ives detailed study, the Mason survey, the IND survey, and 4 relatively recent published series The numbers in the table should not be taken as strictly comparable, as duration of exposure, dose, method of collecting and reporting ADR, etc. varied considerably

TABLE 41 COMPARISON OF ADR

STUDY	IVES DETAILED SURVEY	MASON SURVEY (AT...[1])	HEGER (1983b)	FOGOROS (1983)	PETER (1983)	MCGOVERN (1983b)	IND SURVEY
No Pts (n)	241	1307	196	962	181	80	4802
VA (%)	192 (80)	1085 (83)	196 (100)	779 (81)	139	49 (61)	4249 (88)
SVA (%)	49 (20)	157 (12)	0 (0)	17 (18)	42	31 (39)	553 (12)
Dose Regimen (mg day)							
Load		N/A	800	800 - 1304	Varied[5]	600 - 1200	N/A
Maint	434	443 ± 330[2]		(VA) 628 ± 167 (SVA) 500 ± 183		365 ± 195	
Duration Rx	67 mos	396 days	greater than 16 2 ± 13 0 mo (1 57 mos)	8 ± 7 5 mo (1 day - 27 mos)	3 30 mos	14 8 mo (6 days - 51 mo)	N/A
No Pts w/ADR (%)	175 (73)	N/A	95[6] (48)	662 (73)	ns[7] (175%)	66 (82)	N/A
Ocular	92 (38)		N/A	27 (30)		80 (100)	
Neurol	72 (30)		N/A	18 (20)	30 (17)	19 (24)	
GI	67 28)		N/A	4 (4)		27 (34)	
Skin	44 (18)		19 (10)	20 (22)	21 (12)	11 (14)	
Cardiac	33 (14)		9 (5)	4 (4)	4 (2)	8 (10)	
Pulm	7 (3)		7 (4)	6 (7)	8 (4)	4 (5)	
Others	81 (34)		N/A	23 (25)	82[8]	25 (31)	
No Pts D/C Rx (%)	17 (7)[9]	N/A	21 (11)	14 (16)	3	14 (18)	399 (8)
Pulm	4 (2)		5 (3)	6 (7)	0	4 (5)	79 (2)
Neurol	3 (1)		1 (1)	0	0		71 (2)
Aggrav /Recurrent Arr th	3 ( )		9 (5)	4 (4)	0	4 (5)	63 (2)
GI	2 (1)		4 (2)	0	0	3 (4)	34 (1)
Ocula	2 (1)		[illegible]	0	0		33 (8)
Skin	0		0	0	2		21 (5)
Misc	3 (1)		2 (1)	4 (4)	1	3 (4)	98 (25)

[1] From Mason JW et al (Amiodarone Toxicity Study Group) Circ 72 Suppl III 272 Oct 1985 (Abstr)
[2] 61 pts were treated for greater than 1 week and was used as denominator
[3] Mean Cumulative Dose 164 ± 157g
[4] Fogoros did not use a loading dose regimen for SVA pts
[5] Peter initially did not use a loading dose regimen then a daily loading dose of 1200 1800 mg In addition they used iv amiodarone concomitantly with oral amiodarone
[6] In Heger s study a number of ADRs were collectively reported (N=76)
[7] Not specified in Peter s study i e unclear how many pts had greater than 1 ADR
[8] Includes 74 pts with abnormal liver function tests without clinical symptoms/signs of liver dysfunction
[9] Ten (10) additional patients temporarily discontinued amiodarone

B Adverse Reactions

1 Overview of Adverse Reactions

Adverse reactions were recorded for all patients from the Detailed Study and Global Survey, and the overall incidence is summarized in Table 42

TABLE 42 ADVERSE DRUG REACTION SUMMARY

	Detailed Study	Global Survey
Patients treated	241	4,802
Patients with any ADR	175 (73%)	NA
Patients with severe ADR	28 (12%)	NA
Patients discontinued for ADR	17 (7%)	399 (8%)

NA = not available

Adverse reactions are presented by body system as follows: ocular, neurologic, pulmonary, cardiovascular, gastrointestinal, hepatic, dermatologic, thyroid and miscellaneous. Within each body system, the ADR were grouped by signs/symptoms.

2 Incidence of Adverse Reactions by Body System

In the Detailed Study, the most frequently observed ADR were neurologic followed by ocular and gastrointestinal. The incidence of ADR by body system is listed in Table 43. Of the 241 patients, 223 entered maintenance and 198 had at least 3 months of treatment, 108 at least 6 months and 115 at least 12 months.

TABLE 43 INCIDENCE OF ADR BY BODY SYSTEM (Detailed Study)

Body System	Number of Patients (N=241)
Neurologic	116 (48%)
Ocular	92 (38.2%)
Gastrointestinal	67 (28%)
Dermatologic	44 (18%)
Cardiovascular	33 (14%)
Hepatic	13 (5%)
Respiratory	7 (3%)
Thyroid	6 (3%)
Miscellaneous	62 (26%)

Incidence of ADR by individual body system from the Detailed Study is described below

Ocular Adverse Reactions

Ocular ADR occurred in 85 of 241 patients (35 3%) in the Detailed Study (Because some centers did not routinely monitor for corneal deposits or record them as ADR, the actual incidence of ocular ADR would be expected to be higher.) Visual disturbances associated with corneal deposits were reported in 23 patients (9 5%) Only 2 patients discontinued therapy because of symptomatic corneal deposits The incidence of ocular ADR is summarized in Table 44

TABLE 44 INCIDENCE OF OCULAR ADR
(Detailed Study)

Description of ADR	No Pts (%) (N=241)	No (%) Pt Discont Treatment (N=241)
Corneal Degeneration*	29 (12)	0
Corneal Pigmentation*	26 (10 8)	0
Corneal Deposit - Visual Disturbance	23 (9 5)	2 (0 8)
Others**	7 (2 9)	0
Total	85 (35 3%)	2 (0 8)

*Classified as changes related to corneal microdeposits

**Others ill-defined eye discomfort (2 cases), and one case each of following endothelial corneal dystrophy, corneal opacity, lattice corneal dystrophy, tear film insufficiency, corneal edema

Neurological Adverse Reactions

Among the 241 patients in the Detailed Study, 72 (29 9%) reported neurological ADR, but no patient discontinued treatment for a primary neurological complaint Table 45 summarizes neurological ADR

TABLE 45 INCIDENCE OF NEUROLOGICAL ADR (Detailed Study)

Description of ADR	No Pt (%) (N=241)
Malaise and Fatigue	21 (8 7)
Tremor/abn involl movm	20 (8 3)
Lack of Coordination	14 (5 8)
Abnormal Gait	13 (5 4)
Dizziness and Giddiness	12 (5 0)
Paresthesias	9 (3 7)
Decreased Libido	7 (2 9)
Insomnia	5 (2 1)
Headache	4 (1 7)
Sleep Disturbance	3 (1 2)
Sleep Stage Dysfunction	2 (0 8)
Other*	6 (2 5)
Total	72 (29 9)

*One case each of difficulty in walking, myalgia and myositis, cramp in limb, apnasia, drowsiness, convulsions

Malaise and fatigue, tremor, lack of coordination, abnormal gait, and dizziness were the most frequently observed neurological ADR, exceeding an incidence of 5% This experience, including the observation that these reactions are rarely cause for discontinuation, is similar to that of other observers

Pulmonary Adverse Reactions

Aside from aggravation of arrhythmias, the major life-threatening ADR reported for amiodarone is pulmonary toxicity, which has been reported by many investigators, in some cases, fairly frequently In these cases, a clinical syndrome of progressive dyspnea is accompanied by functional and pathological data showing a pulmonary interstitial process Because of such reports, close attention was given to pulmonary signs/symptoms In addition to data from the Detailed Study, Rakita's review of published cases of pulmonary reactions (1983c) was also included in the following discussion Sanofi Pharmaceuticals (France) compiled worldwide cases (published and unpublished reports as of February 1984) of pulmonary reactions, which were reviewed to supplement the overall U S experience

In the Detailed Study, 7 patients had pulmonary ADR, of whom 2 had pulmonary symptoms due to congestive heart failure and 5 had pneumonitis The incidence of pneumonitis was 2.1% (5 of 241) Of the 5 patients with pneumonitis, amiodarone was discontinued temporarily in 2 patients who were rechallenged and therapy was permanently withdrawn from 3 patients One of the latter patients died 2 months after discontinuing therapy, probably due to pulmonary reaction The death rate due to amiodarone-induced respiratory reaction was thus 1 of 241, or 0 4%

The Global Survey of 4802 patients also provides an approximation of the incidence of pulmonary toxicity Although in the Global Survey adverse effect data were not obtained on patients who continued therapy, it is unlikely that a significant number of these patients had recognized amiodarone-induced pulmonary reactions The experience cited in the literature and also in the Detailed Study show that when pulmonary toxicity is suspected, amiodarone therapy is generally discontinued Combining 95 patients who discontinued therapy and 15 who died of probable amiodarone-induced pulmonary reactions gives an incidence of 110 of 4802 (2 3%) for the Global Survey, similar to the incidence reported above for the Detailed Study The 14% mortality of this ADR when it occurs is also similar to the Detailed Study and compatible with the reports of Heger (1983) who reported 3 deaths in 8 patients with pulmonary toxicity and Fogoros, who found 2 deaths among 6 such patients

Sanofi's review of published and unpublished cases found 102 possible cases as of February 1984, about half (54) of which were considered likely to represent amiodarone toxicity, five of the 54 died at least partly as a result of the pulmonary toxicity Marchlinski (1982) has reported a higher rate of pulmonary toxicity, 4/70 (6%) of a series of 70 patients, including 4/23 (17%) of those at a daily dosage of 400-800 mg and 0/47 of those on 400 mg or less

Of concern is the unusually high rate of 13% pulmonary reactions reported by Mason et al in his survey of over 300 patients The frequency appeared to be related to cumulative dose (or time on drug which increases in approximate proportion to cumulative dose), which could account for lower rates in some series Table 46 shows the rates of certain side effects, including pulmonary, in relation to cumulative dose and to an estimated duration based on a presumed loading dose over two weeks of 15 g and a mean maintenance dose of 450 mg

TABLE 46 RATES OF SIDE EFFECTS IN RELATION TO CUMULATIVE DOSE

Cum Dose (g)	Estimated Duration	n	% of pts with side effects: pulm	CNS	periph neurop	hepatic	visual impair.	arrhyt worsen
0 - 9 9	less than 2 wk	93	0	3.2	1.1	1 1	1.1	4.3
10 - 99 9	less than 2 wk - 29 wk	459	8.3	12.9	4.1	2 2	3.5	1.7
100 - 199 9	29 wk - 61 wk	317	18 9	30.6	8 8	4 1	15.1	0.6
200 - 299 9	61 wk - 92 wk	192	19 3	28.1	11.5	13 5	25.0	1.0
300 - 399.9	92 wk - 124 wk	78	17 9	32.2	7.7	11 5	26 9	2 6
400 - 499 9	124 wk - 156 wk	61	13 1	31.1	6.6	31.1	23.0	1 6
500 - 599.9	156 wk - 315 wk	53	13.2	34 0	11.3	15 1	22 6	0.0
greater than or equal to 1000	greater than 315 wk	1	0.0	100.0	0 0	0 0	100.0	0.0
greater than or equal to 300	greater than 92 wk (21 mos)	193	15 0	32.7	8.3	18 6	24 9	1.0

Obviously patients treated for less than 6 months have a considerably lower rate of most ADRs, including pulmonary (but not worsened arrhythmia, which appears to be an acute response)

Recently, several reports, all abstracts, have examined the frequency of clinical lung disease and/or diffusion abnormalities in patients receiving amiodarone, generally finding higher rates of toxicity and still higher rates of subclinical diffusion abnormality

(1) Magro et al (1985) followed 86 patients for 24 days to 43 months on maintenance doses of 50-600 mg Thirteen (15%) developed dyspnea, cough and infiltrates and either recovered with cessation of amiodarone (11) or died (2). Nine of the 13 cases were documented by a positive gallium scan and histology A variety of pulmonary function tests were observed at baseline and when toxicity appeared, but only baseline diffusion capacity correlated with toxicity. Abnormal baseline was present in 0/8 at baseline, 7/7 tested while toxic showed a reduction from baseline of at least 15%. Abnormal baseline diffusion capacity did not predict toxicity (0 of 18 patients who had less than 60% of normal)

(2) Porterfield et al (1985) found amiodarone pulmonary toxicity in 11/171 (6%) patients followed a mean of 334 days Gallium lung scans in 5 patients all showed abnormalities and patients with preexisting lung disease were said to be at increased risk

(3) Anastasiou-Nana et al (1985) followed 27 patients receiving a mean of 367 mg of amiodarone per day for a median of 17 9 mos, evaluating diffusion capacity, clinical symptoms, and X-rays at baseline and every 3-6 months Ten patients (37%) developed a decrease in diffusion capacity of at least 20% and, of these, three (30% of patients with a 20% or greater fall in diffusion capacity and 11% of all patients) developed overt toxicity (dyspnea, X-ray infiltrates) No patient without a 20% fall in diffusion capacity (0/17) had such toxicity, including 3 who had a 10-20% decrease in diffusing capacity

Cardiovascular Adverse Reactions

Among the 241 patients in the Detailed Study, 33 (13 7%) reported cardiovascular ADR, of whom 6 patients (2 5%) had to discontinue treatment Three of the patients who discontinued treatment (1 2%) had a worsening of their arrhythmia, and one patient each (0 4%) developed sinoauricular node dysfunction, left bundle branch block, and congestive heart failure with chest pain and palpitation, respectively Cardiovascular ADR are summarized in Table 47

TABLE 47 INCIDENCE OF CARDIOVASCULAR ADR (Detailed Study)

Description of ADR	No (%) Total Pts (N=241)	No (%) Pt Discont Treatment (N=241)
Congestive Heart Failure	7 (2 9)	1 (0 4)
Cardiac Arrhythmias	6 (2 5)	3 (1 2)
SA Node Dysfunction	5 (2 1)	1 (0 4)
Hypotension	2 (0 8)	0 (-)
Parox VT	2 (0 8)	0 (-)
Palpitations	2 (0 8)	0 (-)
Circulatory Disease	2 (0 8)	0 (-)
Left BB Block	1 (0 4)	1 (-)
Others*	6 (2 5)	0 (-)
Totals	33 (13 7)	6 (2 5)

*One case each of dyspnea, ventricular fibrillation, 2nd degree AV block, abnormal ECG, premature beats, and chest pain

It is clear, from Table 47, that the 3 most frequent cardiovascular ADR in the Detailed Study were CHF, cardiac arrhythmias and SA node dysfunction. There were no cardiovascular deaths attributed to amiodarone in the Detailed Study

Amiodarone, like other antiarrhythmic agents, has been reported to aggravate arrhythmia in some cases A total of 6 patients had worsening of arrhythmia during amiodarone therapy, 3 were discontinued for ADR and 3 for lack of efficacy Exacerbation of arrhythmia in these patients was observed during the loading phase Of the 6 patients, 5 were taking or had recently discontinued concomitant antiarrhythmics No patient died of amiodarone-associated arrhythmia

The Mason survey also found a low rate (2%) of arrhythmia exacerbation and, not surprisingly, found most in patients who did not take the drug for long Heger (1983) found a 5% rate of exacerbated VT/VF among 196 patients (the patients were apparently identical to those reported by Zipes in Appendix II), including one polymorphic VT associated with prolonged QT Fogoros (1983) found 4 0% of patients with ventricular arrhythmias to worsen with amiodarone and an additional 4% appeared to become refractory to cardioversion (the role of amiodarone was admittedly uncertain in these cases) McGovern (1983) found a 5% rate of worsening overall (8% of patients with ventricular arrhythmias) and noted intractable VT in all, resolving after a few days off drug, no drugs other than digoxin were present

Aside from worsened arrhythmia, severe bradycardia can occur Mason found a 5% rate of bradycardia, McGovern 4% (all of these patients requiring pacing but kept on amiodarone), all of these patients were on digoxin It is possible that amiodarone both depresses the sinus and the automaticity of escape foci

Gastrointestinal Adverse Reactions

In the Detailed Study (N=241), a total of 67 patients (28%) reported gastrointestinal ADR, but only 2 patients (0 8%) discontinued treatment The following table summarizes these ADR

TABLE 48 INCIDENCE OF GASTROINTESTINAL ADR
(Detailed Study)

Description of ADR	Total	No (%) Pt Discont Treatment (N=241)
Nausea and Vomiting	32 (13 3)	1 (0 4)
Constipation	12 (5 0)	0 (0 0)
Anorexia	10 (4 2)	0 (0 0)
Abdominal Pain	5 (2 1)	0 (0 0)
Stomach Function Dis	3 (1.2)	1 (0 4)
Noninfect Gastroenteritis	2 (0 8)	0 (0 0)
Flatul/Eructat/Gas Pain	2 (0 8)	0 (0 0)
Diarrnea	1 (0 4)	0 (0 0)
Total	67 (27 8)	2 (0 8)

Hepatic Adverse Reactions

In the Detailed Study, 13 of 241 patients (5 4%) had a hepatic reaction including 9 with serum enzyme elevations, in only 1 patient (0 4%) was treatment discontinued Results are summarized in Table 49

TABLE 49 INCIDENCE OF HEPATIC ADR (Detailed Study)

Description of Adverse Drug Reaction	No (%) Pts (N=241)	No (%) Pts Treatment Discont
Abnormal Liver Function Tests	9 (3 7)	1 (0 4)
Other Disorders	3 (1 2)	0
Acute Necrosis of Liver*	1 (0 4)	0
TOTAL	13 (5 4)	1 (0 4)

*Patient had elevated liver fun tion tests and biopsy snowing diffuse hepatic parenchymal disease Liver function tests returned to normal and tnen increased again while amiodarone was temporarily withdrawn

Others have reported frequent, mild liver enzyme elevations with occasional, more severe reactions Mason (1985) found some liver injury in 7% of patients, but a severe reaction in only 0 7% Similarly, Fogoros et al (1983) and McGovern et al (1983b) found an 18-20% rate of liver enzyme abnormality but only 1 case each of more severe injury Fogoros' case appeared to be a true drug hepatitis, with transaminase levels well over 1000 The British Committee on Safety of Medicines has reported several cases of irreversible, and ultimately fatal, liver injury

Dermatologic Adverse Reactions

In the Detailed Study, 42 patients experienced dermatological side effects, predominantly photosensitivity (22), but no patient discontinued therapy. ADR are summarized in Table 50 Others have found much higher rates of blue discoloration

TABLE 50 INCIDENCE OF DERMATOLOGICAL ADR (Detailed Study)

Description of ADR	No (%) Pt with ADR (N=241)
Photosensitivity	22 (9 1)
Contusions	3 (1 2)
Alopecia	2 (0 8)
Nonspecific Skin Erupt	2 (0 8)
Pruritus	2 (0 8)
Keratoderma, Acquired	2 (0 8)
Skin Disorder	2 (0 8)
Spontaneous ecchymoses	2 (0 8)
Blue-gray Discoloration	2 (0 8)
Others*	5 (2 1)
Total	44 (18 2)

*One case each of hyperhidrosis, posteruptive color change, onycholysis, nonspecific dermatitis and erythematous reaction

Thyroid Disorders

In the Detailed Study of 241 patients, 4 patients (1 7%) developed hypothyroidism and 2 patients (0 8%) developed thyrotoxicosis, none discontinued therapy Hypothyroidism has been seen more often in some series (11%, Fogoros et al, 4%, Peter et al, 5%, Mason survey) but is readily countered by supplementation Hyperthyroidism is a greater problem and can be grounds for discontinuation

In a recent abstract, Wademanee et al (1985) reported a longitudinal study of 76 patients treated chronically with amiodarone, finding an 8% rate of hypothyroidism, best diagnosed by a finding of TSH greater than 15 microunits/ml, especially with T_4 less than 5 mcg/dl and rT_3 less than 22 ng/dl, and a 2.5% rate of hyperthyroidism best diagnosed by a serum T_3 concentration of more than 200 ng/dl

Miscellaneous Adverse Reactions

Table 51 lists miscellaneous ADR, occurring in a small number of patients which were not classified in any of the body systems described previously

TABLE 51 INCIDENCE OF MISCELLANEOUS ADR (Detailed Study)

Adverse Reaction	Total (%)
Smell/Taste Disturbance	8 (3.3)
Flushing	6 (2.5)
General Symptoms	5 (2.1)
Salivary Secretion	4 (1.7)
Coagulation Defect	3 (1.2)
Edema	3 (1.2)
Integument/Tissue Symptoms	2 (0.8)
Muscle/Ligament Dis	2 (0.8)
Other*	17 (7.5)
Total	50 (20.7)

*Others One patient each - Swelling of limb, pain in joint, osteitis due to other disease, muscle-limb symptom, foreign body in larynx, urination abnormalities, general symptoms, nonspecific head/neck symptoms, abnormal weight gain, goiter, digitalis toxicity, female climacteric, abnormal weight loss, nonspecific joint pain, chest pain, tinnitus, pyrexia of unknown origin

3 Terminations for Adverse Reactions

Amiodarone therapy was withdrawn due to adverse reactions in 399 (8.3%) of the total 4802 patients included in the Global Survey This includes 17 patients (7%, N=241) withdrawn from amiodarone therapy in the 5-center Detailed Study A total of 822 adverse reactions was experienced by these 399 patients, an average of 2.1 symptoms per patient The distribution of these adverse reactions by body system, was as follows

TABLE 52 FREQUENCY OF TERMINATING ADR
(Global Survey)

Body System	Frequency of Terminating ADR	
	Overall*	Primary**
Neurologic	190	71
Cardiovascular	131	97
Respiratory	126	79
Gastrointestinal	125	34
Skin	47	21
Ocular	52	33
Hepatic	39	15
Thyroid	17	15
Miscellaneous	95	34
Total	822	399 (8.3%)

*all symptoms listed for terminating patients
**primary reason for termination

Although neurological ADR were the most frequently cited signs/symptoms, cardiovascular ADR were most frequently cited as the primary cause for termination The high frequency of discontinuation for cardiovascular ADR may reflect the severity of the underlying disease in this patient population ADR pertaining to the skin, eyes or hepatic system were least frequently reported systems both primarily and overall

In these 399 withdrawn patients, the most frequent individual symptoms given as the primary reason for termination are listed in Table 53

TABLE 53 MOST FREQUENT PRIMARY CAUSE FOR TERMINATION

Symptom	Number of Patients	% Treated (N=4802)
Paroxysmal VT	32	0 7
Congestive Heart Failure	27	0 6
Pulmonary Infiltrate	26	0 5
Postinflammatory Pulmonary Fibrosis	22	0.5
Nausea/Vomiting	19	0 4
Cardiac Dysrhythmias nonspec	15	0 3
Visual Disturbances	16	0 3
Other pulmonary (not CHF, infection)	15	0 3
Malaise/Fatigue	14	0 3
Hypothyroidism	13	0 3
Anorexia, "unintentional marasmus," weight loss	11	0 2
Various dermatologic	10	0 2
Solar Dermatitis	9	0 2
Abnormal Involuntary Movement	9	0 2
Peripheral neuropathy/neuritis	9	0 2
Liver injury (drug relationship unknown)	9	0 2
Corneal Deposit	8	0 2
Conduction disorder/AV block	7	0 1
Various visual signs/sympt	7	0.1
Headache	6	0 1
Dizziness/Giddiness	5	0 1
Lack of Coordination	5	0.1
Constipation	5	0 1
Orthostatic Hypotension	4	0 1
SA node dysfunction	4	0 1

In the Detailed Study, although a high percentage of patients reported ADR (175/241, 73%), a low percentage of patients (17/241, 7%) was permanently withdrawn due to ADR Thus, a high percentage of patients experienced ADR but continued to receive amiodarone (158/241, 66%) The ratio of patients experiencing ADR and continuing therapy to those patients withdrawn due to ADR varied with individual body systems Neurological and ocular ADRs occurred frequently in the Detailed Study but caused few withdrawals from therapy In contrast, cardiovascular and respiratory ADR occurred less frequently but caused more withdrawals from therapy

Terminations due to Ocular ADR

Of the 4802 patients treated with amiodarone, 33 (0 7%) discontinued therapy because of ocular ADR, most commonly visual disturbances or distortion (18) probably related to corneal deposits The ocular ADR are summarized in Table 54

TABLE 54 DISCONTINUATION OF AMIODARONE DUE TO OCULAR ADR (Global Study)

Symptom	Total No Pts Discontinued	% of Pts Treated (N=4802)	% of All Pts Discontinued (N=399) **
Visual Disturbances/ Distortions	18	0 4	4 5
Corneal Deposit	8	0 2	2 0
Visual Discomfort	2	0 04	0 5
Pain Around Eye	1	0 02	0 3
Others*	4	0 10	1 3
Total	33	0 7	8 3

*Others - One patient each with acute iridocyclitis, corneal degeneration, toxic optic neuropathy, acute conjunctivitis, tear film insufficiency, corneal opacity, amblyopia

** Therapy was discontinued because of ADR in 399 patients

Terminations due to Neurological ADR

In the Global Survey (N-4802), there were 399 patients who were withdrawn from treatment because of an ADR Of these, 71 patients had a neurological ADR listed as the primary reason for discontinuation. Table 55 gives a breakdown of these neurological ADR

TABLE 55 DISCONTINUATION OF AMIODARONE DUE TO NEUROLOGICAL ADR (Global Survey)

Symptom	No Pts Discontinued	% of Treated (N=4802)	% of All Pts Discontinued (N=399)
Malaise and Fatigue	14	0 29	3 5
Tremor	9	0 19	2 3
Headache	6	0 12	1 5
Lack of Coordination	5	0 10	1 3
Dizziness and Giddiness	5	0 10	1 3
Others*	32	0 67	8 0
Total	71	1 48	17 8

*Included depressive disorders, sleep disorders, decreased libido, anxiety state

It is evident from Table 55 that in the Global Survey, the most frequent neurological symptoms which resulted in discontinuation of amiodarone treatment were malaise/fatigue and tremor

Terminations due to Pulmonary ADR

Of 399 patients whose treatment was discontinued for ADR, 126 were listed as having a respiratory ADR (79 patients with primary as well as 47 with contributory reasons for discontinuation were included) Reviewed in detail, 95 cases were considered as probably amiodarone-induced pulmonary toxicity Of these 95 patients, 16 died (10 were unrelated and 6 related to respiratory ADR) Among the 79 survivors, the respiratory ADR resolved in 33, improved in 32 and remained unchanged in 9 patients, 5 patients were lost to follow-up As noted earlier, rates of pulmonary toxicity (which usually lead to discontinuation) have been reported in the 10-13 range recently

Terminations due to Cardiovascular ADR

Of the 399 patients, 97 discontinued amiodarone therapy because of cardiovascular side effects Table 56 summarizes cardiovascular ADR that prompted withdrawal from amiodarone therapy

TABLE 56 DISCONTINUATION OF AMIODARONE DUE TO CARDIOVASCULAR ADR (Global Survey)

Description of ADR	No Pts Discontinued	% of Treated (N=4602)	% Pts Discontinued (N=399)
Paroxysmal Ventricular Tachycardia	32	0.7	8.0
Congestive Heart Failure	27	0.6	6.8
Cardiac Dysrhythmias	11	0.2	2.8
Others* (frequency less than 10 cases)	27	0.6	6.8
Total	97	2.00	24.3

*Included hypotension, dyspnea, SA node dysfunction, heart block, pulmonary embolism, cardiomegaly