A COMPARISON OF SEVEN ANTIARRHYTHMIC DRUGS IN PATIENTS WITH VENTRICULAR TACHYARRHYTHMIAS

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Abstract *Background.* The relative efficacies of various antiarrhythmic drugs in the treatment of ventricular tachyarrhythmias are not well known. This study examined the effectiveness of imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine, and sotalol in patients with ventricular tachyarrhythmias who were enrolled in the Electrophysiologic Study versus Electrocardiographic Monitoring trial.

Methods. Patients were randomly assigned to undergo serial testing of the efficacy of the seven antiarrhythmic drugs by one of two strategies: electrophysiologic study or Holter monitoring together with exercise testing. The seven drugs were then tested for efficacy in random order in patients who were eligible to receive them. The frequencies of predictions of drug efficacy and of adverse drug effects during the initial drug titration were tabulated for all 486 randomized subjects. Patients received long-term treatment with the first antiarrhythmic drug that was predicted to be effective on the basis of drug testing. Recurrences of arrhythmia, deaths, and adverse drug effects during long-term follow-up were recorded for the 296 patients in whom an antiarrhythmic drug was predicted to be effective.

Results. In the electrophysiologic-study group, the percentage of patients who had predictions of drug efficacy was higher with sotalol (35 percent) than with the other drugs (16 percent, $P<0.001$). There was no significant difference among the drugs in the Holter-monitoring group. The percentage of patients with adverse drug effects was lowest among those receiving sotalol. The actuarial probability of a recurrence of arrhythmia after a prediction of drug efficacy by either strategy was significantly lower for patients treated with sotalol than for patients treated with the other drugs (risk ratio, 0.43; 95 percent confidence interval, 0.29 to 0.62; $P<0.001$). With sotalol, as compared with the other drugs combined, there were lower risks of death from any cause (risk ratio, 0.50; 95 percent confidence interval, 0.30 to 0.80; $P = 0.004$), death from cardiac causes (0.50; $P = 0.02$), and death from arrhythmia (0.50; $P = 0.04$). The cumulative percentage of patients in whom a drug was predicted to be effective and in whom it remained effective and tolerated was higher for sotalol than for the other drugs ($P<0.001$).

Conclusions. Sotalol was more effective than the other six antiarrhythmic drugs in preventing death and recurrences of arrhythmia. In patients similar to those in this study, if antiarrhythmic-drug therapy is to be used to prevent recurrences of ventricular tachyarrhythmias, treatment with sotalol and assessment of its potential efficacy by Holter monitoring are a reasonable initial strategy. (N Engl J Med 1993;329:452-8.)

THE relative efficacy as well as the safety of various antiarrhythmic drugs used to prevent the recurrence of ventricular tachyarrhythmias in susceptible patients has not been rigorously compared. In the Electrophysiologic Study versus Electrocardiographic Monitoring (ESVEM) trial,[1-3] the efficacy of seven antiarrhythmic drugs of different classes was tested in patients with ventricular tachyarrhythmias who were eligible to receive them. Patients were randomly assigned to one of two testing strategies, electrophysiologic study or Holter monitoring, and the seven antiarrhythmic drugs were tested in random order. These patients were then prospectively treated with the first drug predicted to be effective in order to prevent the recurrence of sustained ventricular tachyarrhythmias under standardized conditions. The purpose of this analysis was to compare the seven antiarrhythmic drugs used in the trial with respect to the frequency and accuracy of the predictions of efficacy by electrophysiologic study and Holter monitoring, as well as the long-term tolerance, safety, and efficacy of the drugs.

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METHODS

The design and primary results of the trial have been described in the accompanying article[3] and elsewhere.[1,2] Patients with ventricular tachyarrhythmias were randomly assigned to undergo antiarrhythmic-drug testing by one of two methods: electrophysiologic study or Holter monitoring (in conjunction with exercise testing). Seven antiarrhythmic drugs were studied: imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine, and sotalol. The selection of these drugs, the dosing schedule, and the criteria for the eligibility of patients to receive each drug have been described elsewhere.[1] The randomized patients received up to six drugs in sequence. Those that a patient was eligible to receive were assigned to be tested in random order. Each drug was tested when a specified dose or concentration was reached. If this dose could not be achieved because of intolerance on the patient's part, a lower dose was used as long as it exceeded a specified minimum. Testing was performed once for each drug until one drug was predicted to be effective or all six drugs failed. Patients did not undergo testing of a particular drug if they could not tolerate the minimal dose or had serious ventricular arrhythmia before the efficacy test. Serious ventricular arrhythmia requiring discontinuation of the drug during titration was defined as one of the following: sustained ventricular tachycardia, torsade de pointes ventricular tachycardia, cardiac arrest, symptomatically intolerable ventricular ectopy, or a 10-fold increase in the frequency of ventricular ectopic beats. In this analysis only those adverse events that resulted in the discontinuation of the study drug are presented. Intolerable symptoms of arrhythmia were counted as proarrhythmic effects. In cases of sustained ventricular tachyarrhythmia occurring during drug titration, we did not attempt to differentiate between recurrences of arrhythmia and proarrhythmic drug effects, except in the case of torsade de pointes,

which was considered to be a proarrhythmic effect. Patients received long-term treatment with the first antiarrhythmic drug that was predicted to be effective on the basis of drug testing. The duration of long-term follow-up was 6.2 years. The last end-point event was recorded at 5.4 years of follow-up. During follow-up, sustained ventricular tachyarrhythmias were considered to be recurrences of arrhythmia rather than proarrhythmic effects, except for torsade de pointes, which was tabulated as a recurrence of arrhythmia in the actuarial analyses and a proarrhythmic effect in the analysis of adverse events. Serious arrhythmia that occurred before the patient had received three doses of drug was not considered to require discontinuation of the drug if the investigator thought that insufficient activity of the drug was responsible.

Patients did not receive any drug they had previously received if the drug had been ineffective or had caused adverse effects. Cardiogenic shock or class 4 congestive heart failure as determined according to the symptom-activity scale of Goldman et al.[4] precluded the use of sotalol, propafenone, and mexiletine, although investigators made exceptions when they thought one of these drugs could be used safely. No specific lower limit of left ventricular ejection fraction was established for the use of these drugs. The presence of substantial atrioventricular block precluded the use of mexiletine, propafenone, and pirmenol.

Patients were questioned about possible adverse effects with the aid of a symptom list and a data form, each day during the initial hospitalization and at each subsequent follow-up visit (at one, three, and six months and every six months thereafter). Electrocardiograms, 24-hour Holter recordings, and routine blood tests were obtained at each follow-up visit. Patients who had adverse effects requiring the discontinuation of the drug within the first month after discharge from the hospital were permitted to resume serial drug testing.

Statistical Analysis

Most of the methods of statistical analysis used are described in the accompanying article.[3] The multivariate analyses in the present article were performed in two different ways, as follows: (1) censoring data on patients on the last date they were known to be alive, a method that included time after withdrawal from the study and discontinuation of the drug, and (2) censoring data on patients at the time of study withdrawal or drug discontinuation. The P values comparing the actuarial probabilities of recurrence of arrhythmia or death for sotalol and the other drugs have been adjusted for the influence of the covariates described previously.[3,5-7] Before the trial, our rationale for comparing sotalol with the six other drugs was that those drugs were categorized differently from sotalol in the Vaughan-Williams classification.[8] Sotalol is both a class II and a class III drug, because it is a beta-blocker and because it prolongs the duration of the action potential.[9] The other six agents are class I drugs because of their ability to block the sodium channel. The percentages of patients who had predictions of drug efficacy and who had adverse effects during treatment were compared by standard statistical tests for categorical and continuous data. The cumulative proportions of adverse events and yields of efficacy for sotalol and the other drugs were compared by the log-rank test.[7] The reported P values are two-tailed and were not adjusted for multiple comparisons.

Results

Clinical Characteristics of the Patients

A total of 486 patients underwent serial drug testing by one of the two strategies, and in 296 patients an effective antiarrhythmic drug was identified. The clinical characteristics of the patients with predictions of drug efficacy are shown in Table 1 according to the drug they received during long-term follow-up. There were few significant differences among the patients. An analysis comparing the patients receiving each drug with those receiving the other drugs showed significant differences only in the mean left ventricular ejection fraction for procainamide (lower left ventricular ejection fraction, $P = 0.01$), propafenone (higher left ventricular ejection fraction, $P = 0.002$), and quinidine (lower left ventricular ejection fraction, $P = 0.02$) and in the percentages in whom previous antiarrhythmic-drug therapy had failed (a lower percentage with quinidine, $P = 0.005$, and a higher percentage with sotalol, $P<0.001$).

The reasons patients were considered ineligible to receive the various drugs differed. The majority of those ineligible to receive propafenone and sotalol were considered ineligible for hemodynamic reasons (low left ventricular ejection fraction, symptoms or signs of severe congestive heart failure, or hypotension). In the majority of those who were considered

Table 1. Base-Line Clinical Characteristics of Patients Who Had Predictions of Drug Efficacy.*

Characteristic	All Patients with Predictions	Imipramine	Mexiletine	Pirmenol	Procainamide	Propafenone	Quinidine	Sotalol	P Value†
No. of patients	296	15	56	26	36	43	36	84	—
Mean age (yr)	65.0±10.1	65.2±8.2	63.9±9.8	66.6±11.7	64.1±10.7	64.4±10.5	66.2±8.7	65.3±10.4	0.888
Male sex (%)	86.8	100.0	87.5	88.5	88.9	88.4	94.4	78.6	0.152
Previous MI (%)	80.1	93.3	80.4	69.2	77.8	76.7	86.1	81.0	0.563
Mean LV ejection fraction (%)	33.0±12.2	28.3±10.3	33.9±11.0	35.9±11.4	28.1±12.1‡	38.8±13.7‡	28.6±11.9‡	34.0±11.7	0.001
SAS class >1 (%)	74.3	73.3	73.2	65.4	88.9	74.4	72.2	72.6	0.500
Cardiac arrest at presentation (%)	22.6	26.7	10.7	15.4	25.0	27.9	36.1	22.6	0.125
Unsuccessful previous therapy (%)	63.5	73.3	69.6	57.7	52.8	53.5	41.7§	78.6§	0.002
Beta-blocker use (%)	13.2	6.7	16.1	19.2	8.3	11.6	13.9	13.1	0.852
Median PVC frequency/hr	172.9	258.8	206.6	176.3	156.8	106.6	189.1	170.1	0.089

*Plus–minus values are means ±SD. MI denotes myocardial infarction, LV left ventricular, SAS symptom-activity scale,[4] and PVC premature ventricular complex.
†P values were derived by F test for each variable.
‡P<0.05 for the comparison with the mean value for all other drugs.
§P<0.05 for the comparison with all other drugs.

ineligible to receive mexiletine, procainamide, and quinidine, these drugs had been ineffective previously.

Serial Testing

The results of efficacy testing of individual drugs are shown in Table 2. The number of patients assigned to each drug varied considerably because of differing numbers of patients who had previously received each drug (some drugs had been used on an investigational basis during part or all of the study), varying criteria for exclusion, and the late introduction of certain drugs or their removal from the trial.[1]

There were significant differences among the seven drugs in the percentages of patients receiving predictions of drug efficacy in the electrophysiologic-study group. Sotalol had the highest percentage of patients with predictions of efficacy (35 percent). This drug also had the highest percentage of patients with predicted efficacy overall, regardless of testing method (43 percent). Among the Vaughan-Williams[8] class I drugs, procainamide was predicted to be effective on the basis of electrophysiologic study more often than the others. There were no significant differences among the drugs tested in the Holter-monitoring group.

The drug dosages are shown in Table 3. The mean dosage during long-term therapy was generally slightly lower because the investigators reduced the dose level, within specified guidelines, when there were adverse effects.

Long-Term Drug Efficacy

When they entered long-term follow-up, 296 patients were receiving drugs that were predicted to be effective. Table 4 shows one-year actuarial estimates of the recurrence of arrhythmia in the patients receiving predictions of efficacy for each drug. The first analysis did not censor data on patients who stopped taking the drug or were withdrawn from the study, whereas the second analysis did. Both analyses showed significant differences between sotalol and the other drugs in the recurrence of arrhythmia. There were significant differences between the drugs in the estimates of mortality from any cause, from cardiac causes, and from arrhythmia, but only in the uncensored analysis.

Actuarial curves for the recurrence of arrhythmia and for the three mortality-related end points in patients receiving sotalol as compared with the patients receiving other drugs are shown in Figure 1, without censoring for discontinuation of the drug. The patients receiving sotalol had a significantly lower actuarial probability of a recurrence of arrhythmia (risk ratio, 0.43; 95 percent confidence interval, 0.29 to 0.62; $P<0.001$), death from any cause (risk ratio, 0.50; 95 percent confidence interval, 0.30 to 0.80; $P = 0.004$), death from a cardiac cause (risk ratio, 0.50; 95 percent confidence interval, 0.28 to 0.90; $P = 0.02$), or death from arrhythmia (risk ratio, 0.50; 95 percent confidence interval, 0.26 to 0.96; $P = 0.04$). A similar analysis that was restricted to patients considered eligible to receive sotalol also showed a significantly lower rate of recurrence of arrhythmia in the patients receiving sotalol than in those receiving

Table 2. Results of Testing for Drug Efficacy.

Drug	No. Who Received Drug	No. (%) with Adverse Effects	No. Tested*	Efficacy Predictions		
				Holter Monitoring	Electrophysiologic Study	Both
				percent		
Imipramine	129	55 (43)	71	45	10	21
Mexiletine	226	62 (27)	162	67	12	36
Pirmenol	109	25 (23)	84	55	19	32
Procainamide	158	38 (24)	116	50	26	34
Propafenone	220	58 (26)	160	48	14	28
Quinidine	157	38 (24)	116	59	16	33
Sotalol	234	37 (16)	196	56	35	43
P value	—	—	—	0.347	<0.001	0.015

*Some patients were withdrawn from the drug before efficacy testing for reasons other than the occurrence of an adverse effect.

Table 3. Incidence of Adverse Events Requiring Discontinuation of the Study Drug.*

	Imipramine	Mexiletine	Pirmenol	Procainamide	Propafenone	Quinidine	Sotalol	P Value†
Titration‡								
No. of patients receiving the drug	129	226	109	158	220	157	234	
Mean dose (mg/kg of body weight/day)	2.75	11.37	4.92	56.96	10.83	27.28	5.59	
Adverse events (%)								
Cardiovascular	25	8	16	6	24	13	14	<0.001
All	43	27	23	24	26	24	16	<0.001
Long-term follow-up								
No. of patients receiving the drug§	15	58	27	39	45	38	85	
Mean dose (mg/kg/day)	2.74	10.96	4.67	56.27	10.55	26.39	5.31	
Adverse events (%)								
Cardiovascular	7	2	7	3	11	8	6	0.514
All	13	19	7	31	13	32	7	0.003

*The incidence of adverse events is expressed as a percentage of the number of patients exposed to the drug.

†P values were derived by F test for each variable.

‡Refers to the period before the completion of the efficacy test.

§Some patients had more than one prediction of efficacy.

Table 4. Actuarial Probabilities of a Recurrence of Arrhythmia at One Year for Each of the Study Drugs in the Censored and Uncensored Analyses.*

Drug	Uncensored Analysis			Censored Analysis		
	No. at risk at 1 yr†	Probability of recurrence	P value (vs. sotalol)‡	No. at risk at 1 yr§	Probability of recurrence	P value (vs. sotalol)‡
		percent			*percent*	
Imipramine	6	48±13	<0.001	4	56±14	0.008
Mexiletine	26	50±7	0.03	19	44±7	0.146
Pirmenol	9	60±10	<0.001	9	56±10	<0.001
Procainamide	18	46±8	0.004	10	50±10	0.004
Propafenone	26	38±7	0.007	19	39±8	0.003
Quinidine	18	45±8	0.001	14	40±9	0.002
Sotalol	65	20±4	—	60	21±4	—

*Data on patients were censored when they discontinued the study drug, withdrew from the study, or both. Plus–minus values are means ±SD.

†Refers to the number of patients known to be alive and free of a recurrence of arrhythmia one year after a prediction of efficacy.

‡P values were based on the entire six-year follow-up period and were adjusted for the following covariates: method of testing, presenting arrhythmia, frequency of premature ventricular complex, score on symptom-activity scale of Goldman et al.,[4] enrollment center, underlying cardiac disease, and failure of previous antiarrhythmic therapy.

§Refers to the number of patients known to be alive, free of a recurrence of arrhythmia, and taking the drug that was predicted to be effective one year after a prediction of efficacy.

any of the other drugs ($P<0.001$) and similar mortality trends ($P = 0.02$, $P = 0.03$, and $P = 0.05$ for death from any cause, death from cardiac causes, and death from arrhythmia, respectively). In another analysis, in which patients with left ventricular ejection fractions below 0.25 and those classified as having class 4 heart failure were excluded, there were similar curves with larger P values for recurrence of arrhythmia and death from any cause, from cardiac causes, and from arrhythmia ($P = 0.002$, $P = 0.03$, $P = 0.03$, and $P = 0.05$, respectively).

An analysis in which data on patients were censored if they discontinued the drug predicted to be effective also found lower probabilities of these events among the patients receiving sotalol. The decrease in probability was significant for recurrence of arrhythmia (risk ratio, 0.41; 95 percent confidence interval, 0.27 to 0.61; $P<0.001$) and nearly significant for mortality ($P = 0.07$, $P = 0.06$, and $P = 0.08$ for death from any cause, from cardiac causes, and from arrhythmia, respectively).

There was no significant difference between the two study groups for any one drug with respect to the actuarial probability of a recurrence of arrhythmia. There was also no significant difference between groups for all drugs other than sotalol. These analyses indicate that the accuracy of predictions of drug efficacy was similar with electrophysiologic study and Holter monitoring for each drug and each drug class in the Vaughan-Williams classification (i.e., classes II and III, which include sotalol, and class I, which includes the other six drugs).

Adverse Effects

The percentages of patients who had adverse effects requiring drug discontinuation are shown in Table 3 for each study drug. Patients receiving imipramine had the highest frequency of adverse effects during the titration phase (43 percent). The most prominent (>10 percent) among the early adverse effects were the central nervous system effects of imipramine and mexiletine; the cardiovascular effects of imipramine, pirmenol, propafenone, quinidine, and sotalol; and the gastrointestinal effects of procainamide, mexiletine, and quinidine. In addition, there was a significant difference between the drugs in the percentage of patients who had ventricular tachyarrhythmias during titration. This adverse effect was more frequent in all its forms among the patients who received propafenone. Nearly half these effects occurred within two days of the start of propafenone therapy and therefore did not result from excessively rapid escalation of the dose. The proportion of patients with adverse effects during titration was lowest among those receiving sotalol (16 percent).

Quinidine and procainamide had the highest percentages of patients with adverse effects requiring the discontinuation of the drug during long-term therapy (approximately 31 percent for each). The most prominent such effects were the gastrointestinal effects of quinidine, mexiletine, and procainamide, the central nervous system effects of quinidine, and the cardiovascular effects of propafenone. Sotalol and pirmenol had the fewest long-term adverse effects (7 percent).

The actuarial probability of drug discontinuation because of an adverse effect was significantly lower among the 84 patients with predictions of efficacy who received sotalol than among the 212 patients with such predictions who received the other agents ($P = 0.005$).

Torsade de Pointes

Ten episodes of torsade de pointes were recorded during the entire trial. None of them appeared to be related to an unusually high or low drug dosage. Seven of the episodes occurred during titration, four of them in patients receiving sotalol (1.7 percent of those exposed to that drug), two in patients receiving pirmenol (1.8 percent), and one in a patient receiving quinidine (0.6 percent). All three episodes occurring during long-term follow-up were in patients treated with sotalol (3.5 percent). No patient died as a result of documented torsade de pointes.

Complete Efficacy

We defined complete efficacy as present when the following conditions were met: (1) the drug was tolerated during titration, (2) the drug was predicted to be effective, (3) arrhythmia did not recur, and (4) the drug was not discontinued because of an adverse ef-

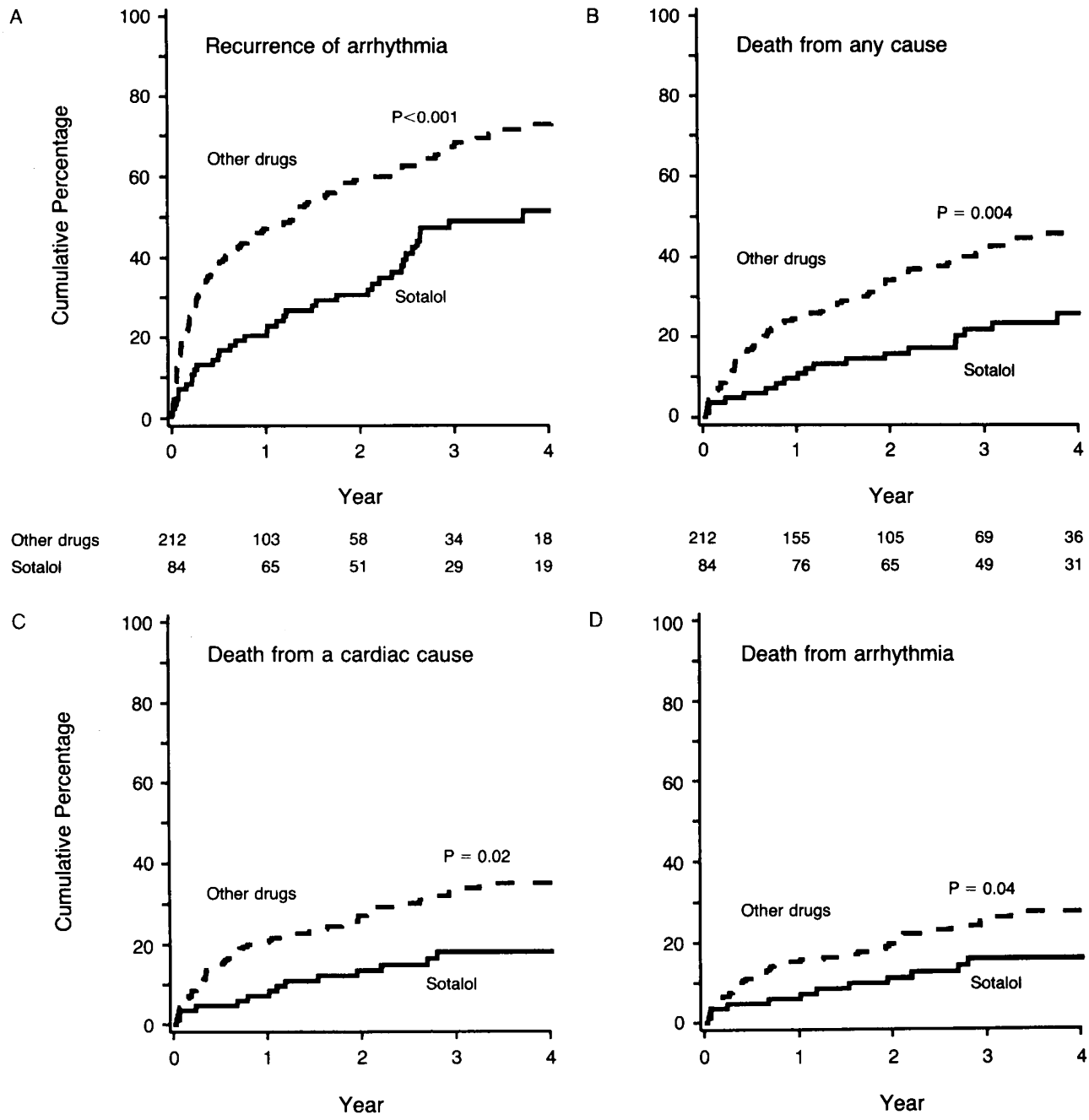

Figure 1. Comparison of Sotalol with the Six Other Drugs with Respect to the Actuarial Probability of the Four End Points in the Patients with Efficacy Predictions.

Cumulative percentages of patients with a recurrence of arrhythmia (Panel A), death from any cause (Panel B), death from a cardiac cause (Panel C), and death from arrhythmia (Panel D) are shown. The P values were determined by multivariate Cox regression. The numbers of patients shown in Panels C and D are the same as those in Panel B. The actuarial display is truncated at 4 years, but the analysis is based on the entire 6.2 years of follow-up.

fect. We defined a drug's yield of complete efficacy as the cumulative proportion of patients who received the drug, received a prediction of efficacy, and continued to use the drug with complete efficacy during follow-up. Figure 2 compares sotalol with the other drugs with regard to the yield of complete efficacy in the electrophysiologic-study and Holter-monitoring groups. The cumulative yields were significantly better for sotalol in both groups. Among the patients who received sotalol, the cumulative yield of complete efficacy showed a trend favoring the Holter-monitoring group as compared with the electrophysiologic-study group ($P = 0.10$).

Discussion

This study demonstrates that sotalol was more effective than six other antiarrhythmic drugs in preventing death and the recurrence of ventricular ar-

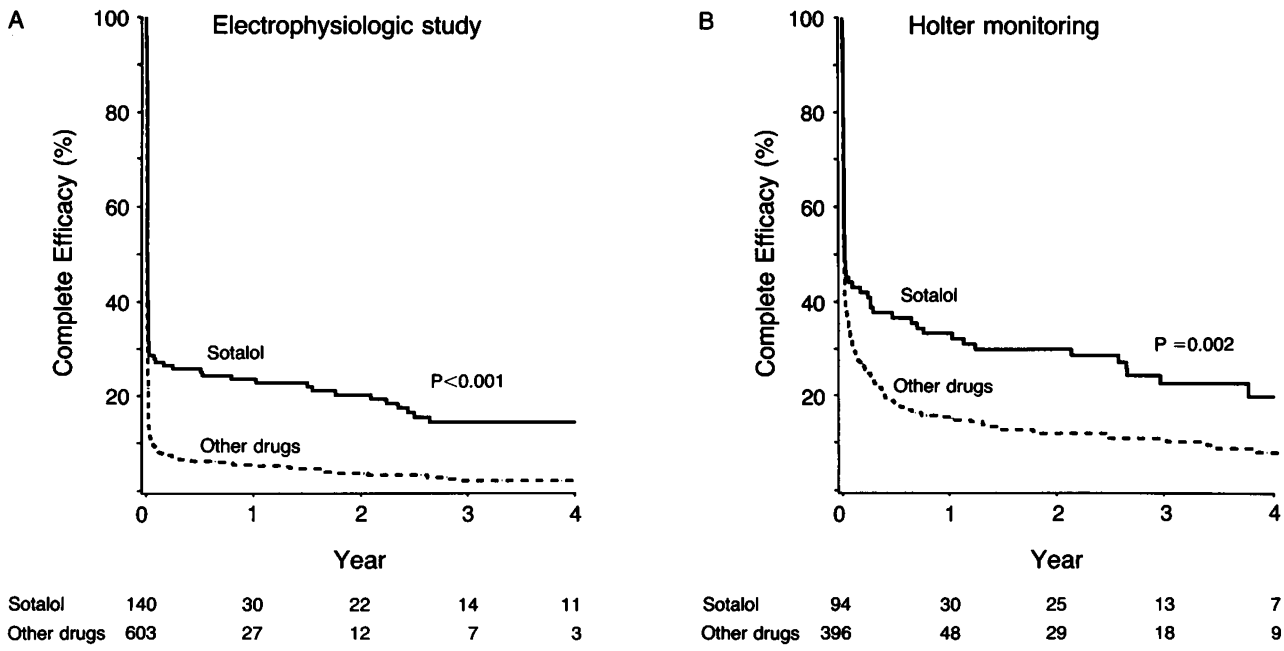

Figure 2. Actuarial Yield of Complete Efficacy.

The cumulative percentage of patients who had complete efficacy of treatment with sotalol is compared with that of patients treated with the other six drugs in the electrophysiologic-study group and the Holter-monitoring group. The P values were determined by the log-rank test.

rhythmias in selected patients with ventricular tachyarrhythmias. There are several differences between sotalol and the other six drugs that may be responsible in part for this superior performance. Beta-blockade may be partly responsible. Sotalol is the only potent beta-blocker among the seven drugs tested. Several trials have shown that beta-blockers reduce mortality after acute myocardial infarction, and some of these trials showed a preferential reduction in the incidence of sudden death.[10-13] The mechanisms responsible for these reductions are not known. Sotalol is the only methanesulfonanilide among the seven antiarrhythmic drugs. Unlike the other drugs, it only inhibits the rapid component of the delayed rectifier potassium current.[14] This may be partly responsible for its superiority. The other six drugs are sodium-channel blockers,[15,16] whereas sotalol is not.[17] It is possible that the absence of sodium-channel–blocking activity gave sotalol an advantage.

Hemodynamic abnormalities led to ineligibility to receive a drug more frequently in the case of sotalol than in the case of the other six drugs. However, the exclusion of patients with severe left ventricular dysfunction and congestive heart failure (those ineligible to receive sotalol) from the actuarial analyses did not eliminate the observed differences in end points between sotalol and the other drugs.

It is noteworthy that treatment of ventricular arrhythmia with sotalol as compared with the other drugs was associated with reduced mortality. As noted above, beta-blockers and possibly amiodarone[18,19] reduce mortality after myocardial infarction, possibly by an antiarrhythmic action. Patients with severe ventricular tachyarrhythmias were excluded from these post-infarction trials, however, and the suppression of arrhythmia in itself was not the primary objective of therapy. The clinical results of treatment with amiodarone in patients with ventricular tachyarrhythmias, as compared with the results of treatment with other drugs, have suggested that amiodarone may improve survival,[20,21] but these results are from studies that were not prospectively controlled with random assignment to antiarrhythmic-drug therapy. A recent prospective, randomized trial comparing the empirical administration of amiodarone with the administration of other drugs on the basis of electrophysiologic study or Holter monitoring[22] showed that a significantly smaller percentage of patients receiving amiodarone reached a combined end point (death from cardiac causes, resuscitation after cardiac arrest, or electrical shock from an implanted defibrillator), but there was no significant difference in mortality between the two groups.

The fact that sotalol was associated with lower mortality in the current study does not prove that it promotes an absolute reduction in deaths, because there was no placebo group in this trial. It is possible that sotalol had no effect on mortality, or even worsened it, but to a lesser degree than the other drugs.

Before beginning our trial, we hypothesized that predictions of efficacy for one or more of the drugs might be more accurate with one testing method than with the other. Our analysis shows that although the percentage of predictions of efficacy differed substantially between the two methods and among the drugs, the accuracy of the predictions for each drug was independent of the testing method. This suggests that for each of the seven drugs we used, equally valid predic-

tions of efficacy can be obtained by either method. The extent, if any, to which this finding can be generalized to other drugs is not known.

Although the accuracy of the predictions of efficacy for each drug was equivalent between the two methods, the yield of complete efficacy, which incorporates both the absence of a recurrence of arrhythmia and the absence of adverse effects requiring the discontinuation of the drug, was higher for sotalol in both study groups and highest in the Holter-monitoring group. The analysis indicates that treating patients with sotalol and testing for efficacy with Holter monitoring yield the largest number of patients treated successfully with the tested drug. In other words, if only one drug among those used in the trial and one method of testing efficacy are to be employed before resorting to other forms of therapy, sotalol and Holter monitoring can be chosen to minimize the number of patients who will require an alternative therapy. For example, our data predict that an initial strategy in which sotalol is administered and its efficacy tested by Holter monitoring will result in efficacious use of sotalol at one year in 33 percent of patients, whereas the use of a class I agent tested by electrophysiologic study will be efficacious in only 5 percent of patients receiving the tested drug at one year. If the efficacy of sotalol is tested by electrophysiologic study, the yield of complete efficacy is predicted to be 23 percent.

Torsade de pointes is a well-known complication of some drugs that prolong ventricular repolarization.[23] Its incidence in our study was low (in 0.8 percent of trials and in 2.1 percent of patients) and was limited to three drugs (quinidine, pirmenol, and sotalol), only one of which (sotalol) caused torsade de pointes during long-term therapy. Since the diagnosis of torsade de pointes requires electrocardiographic documentation, its occurrence during outpatient therapy is probably underestimated. Nevertheless, only two episodes of torsade de pointes were documented in patients who had been discharged from the hospital with a prediction of drug efficacy.

In drawing conclusions about the comparison of the seven drugs in this trial, it is important to recognize that many uncontrolled factors determined whether patients received a given drug and whether they took the drug during long-term follow-up. This was not a truly randomized comparison of the drugs. In addition, the number of patients who received some of the drugs during long-term follow-up was small, limiting the strength of some comparisons. Those observations require corroboration. In addition, it should be recognized that the findings in this study may not apply to all patients with ventricular tachyarrhythmia, as is discussed in the accompanying paper.[3] Also, since many patients in this trial had already had experience with drug inefficacy, often with class I antiarrhythmic agents, our findings may be less relevant in patients who have never been treated.

Recognizing these limitations, we offer a clinical recommendation. In patients with clinical characteristics similar to those of our study population, if antiarrhythmic-drug therapy is to be used to prevent the recurrence of ventricular tachyarrhythmias, treatment with sotalol and assessment of its potential efficacy by Holter monitoring are a reasonable initial strategy.

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