

## PREVENTION OF IMPLANTABLE-DEFIBRILLATOR SHOCKS BY TREATMENT WITH SOTALOL

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**ABSTRACT**

**Background** Patients with implantable cardioverter-defibrillators often receive adjunctive antiarrhythmic therapy to prevent frequent shocks. We tested the efficacy and safety of sotalol, a beta-blocker with class III antiarrhythmic effects, for this purpose.

**Methods** In a multicenter trial, patients were stratified according to left ventricular ejection fraction ( $\leq 0.30$  or  $> 0.30$ ), randomly assigned to double-blind treatment with 160 to 320 mg of sotalol per day (151 patients) or matching placebo (151 patients), and followed for 12 months. Kaplan-Meier analyses of the time to an event were performed. Three end points were used: the delivery of a first shock for any reason or death from any cause, the first appropriate shock for a ventricular arrhythmia or death from any cause, and the first inappropriate shock for a supraventricular arrhythmia or death from any cause.

**Results** Compliance with double-blind treatment was similar in the two groups. There were seven deaths in the placebo group and four in the sotalol group. As compared with placebo, treatment with sotalol was associated with a lower risk of death from any cause or the delivery of a first shock for any reason (reduction in risk, 48 percent;  $P < 0.001$  by the log-rank test), death from any cause or the delivery of a first appropriate shock (reduction in risk, 44 percent;  $P = 0.007$ ), or death from any cause or the delivery of a first inappropriate shock (reduction in risk, 64 percent;  $P = 0.004$ ). Sotalol also reduced the mean ( $\pm$ SD) frequency of shocks due to any cause ( $1.43 \pm 3.53$  shocks per year, as compared with  $3.89 \pm 10.65$  in the placebo group;  $P = 0.008$ ). In the sotalol group, the reduction in the risk of death from any cause or the delivery of a first shock for any reason did not differ significantly between patients with ejection fractions of more than 0.30 and those with ejection fractions of 0.30 or less.

**Conclusions** Oral sotalol was safe and efficacious in reducing the risk of death or the delivery of a first defibrillator shock whether or not ventricular function was depressed. (N Engl J Med 1999;340:1855-62.)

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**A**LTHOUGH implantable cardioverter-defibrillators are effective in terminating ventricular tachyarrhythmias and preventing sudden death from cardiac causes, patients with defibrillators often receive adjunctive antiarrhythmic-drug therapy to reduce the frequency of high-voltage shocks.<sup>1,2</sup> The aim of adjunctive drug therapy is to prevent both appropriate shocks triggered by ventricular tachyarrhythmias and inappropriate shocks triggered by supraventricular tachyarrhythmias. Also, some antiarrhythmic drugs such as sotalol may reduce the defibrillation threshold and improve the responsiveness to shocks.<sup>3</sup>

Studies that have assessed ways to prevent sudden death from cardiac causes indicate that drugs targeting predominantly sodium channels (class I agents) may have unfavorable proarrhythmic effects.<sup>4,5</sup> Class III agents, which prolong the action potential and refractoriness of cardiac tissues, have emerged as the antiarrhythmic agents of choice for managing life-threatening ventricular arrhythmias.<sup>5-8</sup> However, the efficacy and safety of these agents in patients who have received implantable cardioverter-defibrillators have not been tested in randomized, double-blind trials.

Sotalol is an antiarrhythmic agent with both class III and nonselective beta-blocker actions.<sup>9</sup> We evaluated the efficacy and safety of sotalol for the prevention of appropriate and inappropriate shocks delivered to patients who have received implantable defibrillators.

**METHODS****Patients**

Patients were recruited from U.S. and European centers. Men and women who were at least 18 years old were eligible for the study if they had a history of life-threatening ventricular tachyarrhythmias that were not due to a reversible cause; had received their first or a replacement implantable cardioverter-defibrillator within three months before enrollment (patients with replacement defibrillators had to have received at least one shock during the preceding six months); had a defibrillator that provided tiered therapy with electrogram storage and separate logging of shocks

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and antitachycardia pacing episodes; had undergone successful defibrillation at the time of implantation, with shock energies at least 10 J below the maximal defibrillator output; and provided informed consent. Patients were excluded from the study if they had incessant ventricular tachycardia; had received antiarrhythmic-drug therapy fewer than five half-lives of the drug before randomization in the case of class I and III agents (and less than three months before randomization in the case of amiodarone); had a QT interval of more than 450 msec (or a JT interval of more than 360 msec) in the absence of drug therapy; had a long-QT syndrome, including prolongation of the QT interval in response to specific drugs; had unstable coronary syndromes or had had an acute myocardial infarction less than two weeks before screening; had intractable heart failure (New York Heart Association class IV); were candidates for heart transplantation; or had a medical condition that was likely to be fatal in less than two years.

### Study Design

This was a double-blind, placebo-controlled, parallel-group, stratified multicenter trial. Patients meeting the entry criteria were assigned to treatment with racemic (*d,l*-) sotalol (Betapace, Berlex Laboratories, Montville, N.J.) or matching placebo according to a computer-generated random code, with blocked stratification according to the left ventricular ejection fraction ( $\leq 0.30$  or  $> 0.30$ ) at each site.<sup>10</sup> The initial dosage of sotalol was 120 mg twice daily. After patients had received at least four doses, an electrophysiologic study was performed while they were hospitalized to test the effect of treatment on the inducibility of ventricular fibrillation or tachycardia and the preservation of a minimal defibrillation safety margin of 10 J.

Follow-up lasted 12 months, with scheduled visits 1, 3, 6, 9, and 12 months after discharge. An additional visit was required if a patient's cardioverter-defibrillator had delivered a shock. At all visits, the cardioverter-defibrillators were assessed, and the list of shocks and pacing episodes was printed out. Investigators were permitted to adjust the dose of either sotalol or placebo to a minimum of 80 and a maximum of 160 mg twice daily to optimize efficacy and avoid toxic effects, including excessive bradycardia (defined as a daytime heart rate below 50 beats per minute), an excessively prolonged QT interval (more than 500 msec) or JT interval (more than 410 msec), and signs of worsening heart failure. If signs of excessive beta-blockade occurred during concomitant therapy with beta-blockers, the recommended initial adjustment was to reduce or omit the administration rather than to change the study-drug treatment. When creatinine clearance was reduced to 30 to 60 ml per minute, the same doses were given, but they were given only once daily. The doses of the study drug and all other drugs, as well as the date of their initiation and termination, were entered in medication-report forms. Compliance with treatment was monitored by tablet counts at each clinic visit.

Adverse events requiring the discontinuation of treatment included new-onset, incessant ventricular tachycardia, torsade de pointes, supraventricular arrhythmias requiring treatment with an antiarrhythmic agent other than beta-blockers or calcium-channel blockers, prolongation of the QT interval beyond 500 msec despite a reduction (in a double-blind fashion) of the dose of the study drug, a creatinine clearance rate below 30 ml per minute, explantation of the defibrillator, or symptoms and signs judged by the investigator to indicate toxicity or inefficacy of the study drug (the need for frequent shocks from the defibrillator). The treatment code could be broken only in the event of a medical emergency requiring knowledge of the patient's treatment history. For the purpose of the intention-to-treat analysis, patients who discontinued treatment prematurely were followed for the rest of the 12-month period, during which treatment with sotalol was not permitted. Concomitant treatment with antiarrhythmic drugs other than beta-blockers, calcium-channel blockers, and digoxin was not allowed.

The primary end point was death from any cause or the delivery of a first shock for any reason (except as a result of electro-

physiologic testing); end points were also analyzed according to the appropriateness of a first shock: those delivered as a result of ventricular tachycardia or fibrillation were deemed appropriate, and those delivered in response to supraventricular arrhythmias or other events (i.e., instrumental problems) were deemed inappropriate. The designation of shocks as appropriate or inappropriate was performed by the investigators without knowledge of a patient's treatment assignment on the basis of device-derived data including the heart rate, the variability of the rate, and morphologic findings on electrograms. A secondary end point was the frequency of shocks due to any cause, defined as the number of shocks delivered during the 12-month follow-up.

### Statistical Analysis

Analyses were performed both according to the intention to treat and according to actual treatment. The intention-to-treat analysis included all events that occurred during the 12-month period after the first dose of the study drug, irrespective of the duration of treatment. Patients were considered to have stopped treatment one week after they received the last dose of the study drug. Continuous variables were compared by one-way analysis of variance or Wilcoxon's rank-sum test for unpaired samples, and categorical variables were compared by chi-square or Fisher's exact tests. Time-to-event curves describing the proportion of patients who remained event-free during the 12-month period, according to treatment group and ejection fraction, were calculated by the Kaplan-Meier method and compared with the use of log-rank tests. The Cox proportional-hazards model was used to calculate relative risk, adjusted for ejection fraction. All tests were two-tailed and were performed with use of PC SAS software.<sup>11</sup>

## RESULTS

### Randomization

We enrolled 302 patients from 41 U.S. centers and 3 European centers; 151 patients were randomly assigned to each group with stratification according to the ejection fraction. The two treatment groups were well matched at base line (Table 1).

### Compliance with Treatment

The mean ( $\pm$ SD) and median daily doses of sotalol during treatment were  $207 \pm 55$  mg (range, 80 to 320) and 242 mg, respectively. Treatment lasted less than 12 months in 51 patients (34 percent) assigned to receive sotalol and 53 patients (35 percent) assigned to receive placebo. Treatment was stopped early because of adverse events in 27 percent of the patients assigned to sotalol, because of lack of efficacy in 3 percent, and for other reasons in 4 percent. In the placebo group, the respective values were 12, 14, and 9 percent. Therefore, in the sotalol group, treatment was discontinued more often because of adverse events than because of a lack of efficacy, whereas these factors had a roughly equal influence in the placebo group.

### Concurrent Drug Therapy

Table 2 compares the use of concurrent drug therapy during hospitalization after the patients had received at least four doses of the study drug and at the end of the scheduled 12 months of treatment or when treatment was discontinued. Soon after the initiation of treatment, 28 and 27 percent of the pa-

tients were receiving beta-blockers other than sotalol in the placebo and sotalol groups, respectively. At the end of treatment, the rate of use of concurrent beta-blocker therapy was 37 percent in the placebo group and 23 percent in the sotalol group ( $P=0.01$ ). During concomitant beta-blocker therapy, more patients in the placebo group discontinued the study drug (17 of 53, or 32 percent) than in the sotalol group (8 of 51, or 16 percent;  $P=0.05$ ). During follow-up, the rate of treatment with digoxin, diuretics, or angiotensin-converting-enzyme inhibitors did not differ significantly between the two groups. The rate of administration of these drugs in combination, a regimen frequently used for the treatment of heart failure, was also similar in the two groups (Table 2).

**Deaths**

Four patients in the sotalol group died: two of heart failure and two of noncardiac causes (ischemic colitis and complications of aortic aneurysmectomy). Two of the deaths (one due to heart failure and one to ischemic colitis) occurred during double-blind treatment. Seven patients in the placebo group died; three deaths were related to cardiac causes (heart failure in two patients and coronary bypass in one patient), and four were due to other causes (pneumonia in three patients and massive pulmonary embolism in one patient). Two of the deaths (one patient from heart failure and one from pulmonary embolism) occurred during double-blind treatment.

**Outcome of Therapy According to the Intention to Treat**

The Kaplan–Meier time-to-event curves for the end point of death from any cause or the delivery of a shock for any reason differed significantly between the groups ( $P<0.001$  by the log-rank test) (Fig. 1). According to the Kaplan–Meier estimates, 66 percent of patients in the sotalol group and 46 percent of patients in the placebo group had not reached this end point at 12 months (Table 3). This difference corresponds to a reduction in risk of 48 percent with sotalol treatment (relative risk of reaching the end point in the sotalol group as compared with the placebo group, after adjustment for left ventricular ejection fraction, 0.52; 95 percent confidence interval, 0.37 to 0.74). For the end point of death from any cause or the delivery of an appropriate first shock for ventricular tachyarrhythmias, the Kaplan–Meier curves differed throughout the 12-month period ( $P=0.007$  by the log-rank test) (Fig. 2A). According to the Kaplan–Meier estimates, 73 percent of patients in the sotalol group and 58 percent of patients in the placebo group had not reached the end point at 12 months (Table 4). This difference corresponds to a reduction in risk of 44 percent with sotalol treatment (relative risk, 0.56; 95 percent confidence interval, 0.36 to 0.85). The Kaplan–Meier estimates of survival without the delivery of an inap-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	PLACEBO (N=151)	SOTALOL (N=151)
Age — yr	61±11	63±11
Sex — no. (%)		
Male	124 (82)	127 (84)
Female	27 (18)	24 (16)
Left ventricular ejection fraction†		
Mean — %	39±14	37±12
≤30% — no. (%)	51 (34)	52 (34)
>30% — no. (%)	99 (66)	99 (66)
New York Heart Association class — no. (%)		
I	85 (56)	87 (58)
II	60 (40)	54 (36)
III	6 (4)	10 (7)
Blood pressure — mm Hg		
Systolic	125±19	124±20
Diastolic	71±12	71±11
Previous myocardial infarction — no. (%)	100 (66)	110 (73)
Coronary bypass operation — no. (%)	60 (40)	55 (36)
Angioplasty — no. (%)	42 (28)	34 (23)
Heart rate — beats/min	74±13	74±13
QT interval — msec	394±39	400±44
Indication for implantable defibrillator — no. (%)		
Near-fatal arrhythmia	48 (32)	59 (39)
Symptomatic or inducible ventricular tachyarrhythmia	103 (68)	92 (61)

\*Plus-minus values are means ±SD. Because of rounding, percentages may not total 100. None of the differences between groups were significant ( $P>0.1$ ).

†The ejection fraction was not available for one patient.

**TABLE 2. CONCURRENT DRUG THERAPY DURING DOUBLE-BLIND TREATMENT AND AT THE END OF TREATMENT.**

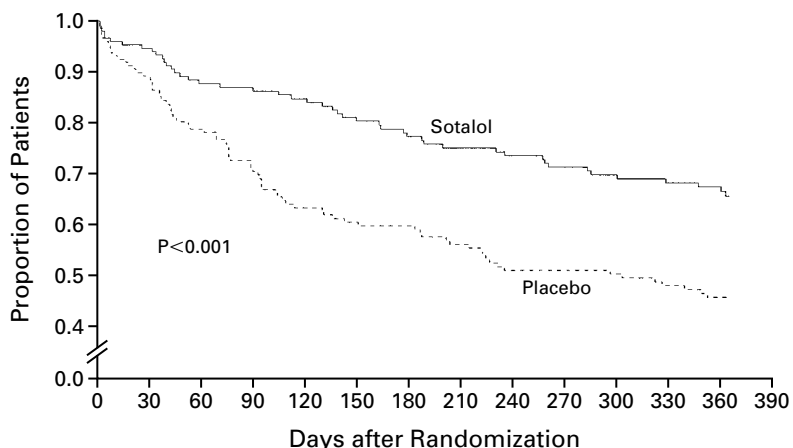
DRUG*	PLACEBO		SOTALOL	
	AT START OF TREATMENT (N=151)†	AT END OF TREATMENT (N=143)‡	AT START OF TREATMENT (N=151)†	AT END OF TREATMENT (N=142)‡
	percentage of patients			
Beta-blocker	28	37	27	23§
Calcium-channel blocker	21	27	19	23
Digoxin	38	44	35	37
Diuretics	39	52	38	48
ACE inhibitors	54	69	64	71
Digoxin, diuretic, and ACE inhibitor	19	27	15	19
Hypolipidemic agent	22	36	27	38

\*ACE denotes angiotensin-converting enzyme.

†Patients were assessed while they were hospitalized after they had received at least four doses of the study drug.

‡Patients were assessed at the end of the scheduled 12 months of treatment or when they discontinued treatment.

§ $P=0.01$  by the chi-square test for the comparison with the placebo group at the end of treatment. None of the other differences between groups were significant.



No. AT RISK	
Placebo	151 129 114 101 90 84 84 77 70 70 69 65 49
Sotalol	151 136 123 119 115 109 104 101 99 95 91 90 70

**Figure 1.** Time to Death from Any Cause or the Delivery of a First Shock for Any Reason, According to the Intention to Treat.

The log-rank test was used to calculate the P value.

appropriate shock for supraventricular arrhythmias at 12 months were 93 percent in the sotalol group and 81 percent in the placebo group; this difference corresponds to a reduction in risk of 64 percent with sotalol treatment (relative risk, 0.36;  $P=0.004$  by the log-rank test). Six patients in the sotalol group and five in the placebo group received an inappropriate first shock owing to various instrumental difficulties. The mean frequency of the delivery of a shock for any reason was significantly lower in the sotalol group than in the placebo group ( $1.43 \pm 3.53$  vs.  $3.89 \pm 10.65$  shocks in the 12-month period,  $P=0.008$  by the Wilcoxon rank-sum test).

Stratification according to the left ventricular ejection fraction ( $\leq 0.30$  or  $> 0.30$ ) revealed significant treatment effects in both strata. According to Kaplan-Meier estimates in the group with ejection fractions of 0.30 or less, the likelihood of survival without the delivery of a first shock for any reason was higher in the sotalol group than in the placebo group (61 percent vs. 38 percent,  $P=0.02$  by the log-rank test). The relative risk of reaching the end point in the sotalol group was 0.49 (95 percent confidence interval, 0.28 to 0.88). In the group with ejection fractions of more than 0.30, the likelihood of survival without the delivery of a first shock for any cause was also higher in the sotalol group than in the placebo group (69 percent vs. 50 percent,  $P=0.005$  by the log-rank test). The relative risk of reaching the end point in the sotalol group was 0.52 (95 percent confidence interval, 0.32 to 0.82). In the sotalol group as a whole, the relative risk of reaching the end point did not differ significantly between the group with ejection fractions of 0.30 or less and the group with ejection fractions of more than 0.30 ( $P=0.45$ ).

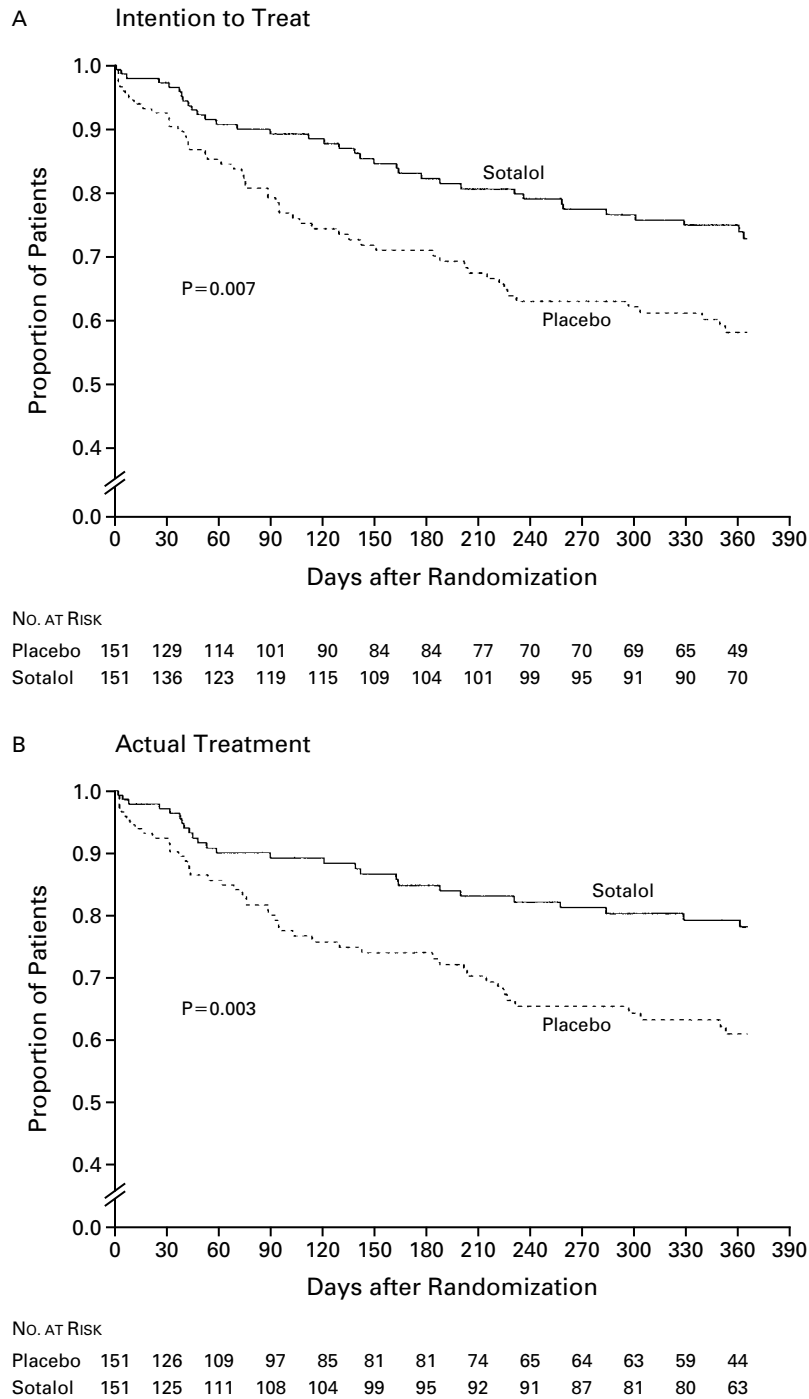
The use of beta-blockers other than sotalol had no significant effect on the risk of death or the delivery of a first shock for any reason. The risk in the group receiving sotalol and beta-blockers was 53 percent lower than that in the group receiving placebo and beta-blockers. The risk in the group receiving sotalol alone was 46 percent lower than that in the group receiving placebo alone. These reductions in risk did not differ significantly ( $P=0.38$ ).

**TABLE 3.** OUTCOME ACCORDING TO THE INTENTION-TO-TREAT ANALYSIS.

VARIABLE	PLACEBO	SOTALOL
	(N=151)	(N=151)
	number (percent)	
Death from any cause	7 (5)	4 (3)
Delivery of a first shock for any reason*	73 (48)	45 (30)
Kaplan-Meier estimate of survival free of shock for any reason	74 (46)	104 (66)†

\*Three patients in the placebo group and two in the sotalol group received a first shock for any reason before they died.

† $P < 0.001$  by the log-rank test.



**Figure 2.** Time to Death or the Delivery of an Appropriate First Shock for Ventricular Tachyarrhythmia, According to the Intention to Treat (Panel A) and Actual Treatment (Panel B). The log-rank test was used to calculate the P values.

**TABLE 4. INTENTION-TO-TREAT ANALYSIS OF DEATH FROM ANY CAUSE OR DELIVERY OF AN APPROPRIATE FIRST SHOCK FOR VENTRICULAR TACHYARRHYTHMIA.**

VARIABLE	PLACEBO	SOTALOL
	(N=151)	(N=151)
	number (percent)	
Death from any cause	7 (5)	4 (3)
Delivery of an appropriate first shock*	49 (32)	33 (22)
Death from any cause or delivery of an appropriate first shock	53 (35)	35 (23)
Kaplan–Meier estimate of survival free of an appropriate first shock or death from any cause	98 (58)	116 (73)†

\*Three patients in the placebo group and two in the sotalol group received a first shock for any reason before they died.

†P=0.007 by the log-rank test.

**TABLE 5. ADVERSE EVENTS.**

EVENT	PLACEBO	SOTALOL
	(N=151)	(N=151)
	number (percent)	
Dizziness	38 (25)	39 (26)
Fatigue	29 (19)	34 (23)
Anxiety	15 (10)	8 (5)
Dyspnea	21 (14)	26 (17)
Peripheral edema	11 (7)	7 (5)
Pulmonary edema	1 (1)	1 (1)
New or worsening heart failure	14 (9)	21 (14)
Postural hypotension	3 (2)	4 (3)
Bradycardia	3 (2)	13 (9)
Heart block	1 (1)	0
Prolongation of QT interval	0	5 (3)
Torsade de pointes	1 (1)	1 (1)
Chest pain	16 (11)	21 (14)
Myocardial infarction	3 (2)	1 (1)
Coronary revascularization	4 (3)	6 (4)

Furthermore, the Kaplan–Meier estimates of the likelihood of remaining event-free at 12 months in the placebo group were nearly identical among those who received beta-blockers and those who did not (46.6 percent vs. 45.4 percent).

#### Outcome According to Treatment Received

The results of analysis according to treatment received were similar to those calculated according to

the intention to treat. The Kaplan–Meier curves for the end point of death or the delivery of an appropriate first shock for any reason differed significantly between the groups (P=0.003 by the log-rank test) (Fig. 2B).

#### Adverse Events

Adverse events typical of those ascribed to beta-blocker therapy, such as dizziness, fatigue, dyspnea, and heart failure,<sup>9</sup> were frequent in both groups (Table 5). Bradycardia, which was more common in the sotalol group than in the placebo group, led to discontinuation of treatment in only two patients, both of whom were assigned to receive sotalol. Treatment was discontinued in three patients in each group because of worsening heart failure. Torsade de pointes was rare, occurring in only one patient in each group (Table 5).

#### DISCUSSION

We found that treatment with sotalol in recommended dosages reduced the probability of the delivery of first shocks in patients who had received an implantable cardioverter–defibrillator for life-threatening arrhythmias. This reduction did not depend on the categorization of the reason for the delivery of the shock, since the reduction was still apparent whether the shocks were analyzed as a whole or according to whether they were delivered appropriately in response to ventricular fibrillation or tachycardia. In addition, treatment with sotalol significantly reduced the risk of the delivery of an inappropriate first shock in response to supraventricular arrhythmias. This finding is in accord with the known efficacy of sotalol for the treatment of supraventricular tachyarrhythmias.<sup>9,12</sup>

An important rationale for adjuvant therapy with antiarrhythmic drugs in patients with implantable cardioverter–defibrillators is that defibrillators do not provide absolute protection against death from arrhythmia. Analysis of large data bases reveals that about 2 percent of episodes of ventricular tachyarrhythmias are refractory to appropriate defibrillator therapy.<sup>13</sup> Recent studies suggest that episodes of ventricular fibrillation, even ones that are successfully terminated by implantable cardioverter–defibrillators, may increase the risk of myocardial<sup>14,15</sup> and cerebral ischemic<sup>16,17</sup> injury. The avoidance of frequent shocks is crucial for the safety and quality of life of patients with implantable cardioverter–defibrillators. An important complication of shocks delivered by implantable defibrillators is that they may evoke serious psychological reactions in up to one third of patients.<sup>18,19</sup>

In our study, the use of beta-blockers other than sotalol did not significantly influence the outcome in either group. Recent overviews of beta-blocker trials suggest that these agents prevent sudden death

from cardiac causes in patients with recent myocardial infarction.<sup>20</sup> The efficacy of beta-blockers in preventing sudden death in patients with heart failure but without recent myocardial infarction is being evaluated in several large trials. A meta-analysis of 18 studies examining the effects of beta-blockers on the survival of patients with heart failure found a non-significant overall reduction of 16 percent in the risk of sudden death.<sup>21</sup> There is evidence that beta-blockers enhance the salutary effects of class III agents, amiodarone in particular,<sup>22,23</sup> and neutralize the proarrhythmic effects of class I agents.<sup>7</sup> In two controlled trials of implantable defibrillators,<sup>1,2</sup> beta-blockers were administered more frequently to patients who were randomly assigned to defibrillator therapy than to those who were assigned to drug treatment (mostly with amiodarone), an imbalance that might have contributed to the superiority of the defibrillators. However, on the basis of Cox regression analyses, the investigators in both trials concluded that beta-blockers had not appreciably influenced the outcome — a result that agrees with ours.

The results of our study suggest that implantable defibrillators provide a unique tool for the testing of antiarrhythmic agents under controlled conditions. Trials of the efficacy of antiarrhythmic drugs for the prevention of sudden death from cardiac causes were conducted without the use of placebo as a control.<sup>5,6,8</sup> For ethical reasons, placebo-treated groups were omitted, although they appear essential for a comparison of drugs that exert both beneficial and detrimental (proarrhythmic) effects. Another serious difficulty in evaluating the efficacy of antiarrhythmic agents in conventional trials is the lack of an effective method for monitoring the occurrence of arrhythmia over the long term. Although implantable defibrillators provide a safety net for testing antiarrhythmic agents, it remains to be defined to what extent prevention of appropriately delivered shocks in response to ventricular fibrillation or fast tachycardia can be used as a surrogate end point or index of the likelihood of death from arrhythmia.<sup>24</sup> There is general agreement that at least some episodes of fast ventricular tachyarrhythmias would not be fatal in the absence of defibrillator therapy, because spontaneous recovery from severe ventricular tachyarrhythmias is possible and because favorable circumstances may allow delivery of lifesaving emergency treatment.<sup>24</sup>

We had difficulty recruiting patients for the study, and most investigators were unable or unwilling to enroll patients in a consecutive manner. In addition, not all centers kept consistent logs of screened patients who were eligible but not enrolled. Therefore, we do not know whether the patients who were enrolled were representative of the population of defibrillator recipients at each center. Nevertheless, the clinical characteristics of the patients were very similar to those reported in studies of large

data bases,<sup>13</sup> a meta-analysis of 18 studies,<sup>25</sup> and a controlled trial.<sup>2</sup>

Compliance with treatment was similar in the sotalol and placebo groups. The avoidance of high doses of sotalol (maximal dose, 320 mg per day; mean, 207 mg per day), in contrast to some early trials in which daily doses of 640 mg or more were given,<sup>9</sup> is likely to have contributed to this finding. However, the rates of discontinuation of treatment were similar and relatively high in both groups: about 33 percent at one year. We believe that difficulties in recruiting participants and the high rates of discontinuation in both study groups are partly attributable to the demanding character of the protocol. Patients recovering from life-threatening episodes of ventricular arrhythmia, whether or not there was a need for resuscitation, are reluctant to accept the possibility of receiving placebo instead of active drug. Prescribing placebo to patients known to be at risk for sudden death poses ethical and medicolegal questions, particularly because available evidence suggests that some antiarrhythmic agents prevent lethal arrhythmias.<sup>8,26</sup> Electrophysiologists are used to adjusting therapy in response to the arrhythmic events experienced by their patients. These considerations may help to explain why investigators had a relatively low threshold for abandoning double-blind therapy when adverse events occurred.

In summary, we found that treatment with the oral antiarrhythmic agent sotalol reduces the probability of the delivery of an appropriate first shock or a first shock for any reason among patients who have received implantable cardioverter-defibrillators. Sotalol also prevented the occurrence of shocks in response to supraventricular arrhythmias, a frequent cause of inappropriate defibrillator therapy. Treatment with sotalol was equally effective in the presence and absence of a depressed left ventricular ejection fraction. These findings suggest that sotalol is useful for patients undergoing defibrillator therapy.

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## APPENDIX

In addition to the authors, the following investigators also participated in the study: *St. Luke's Medical Center, Milwaukee* — M. Akhtar; *LDS Hospital, Salt Lake City* — J. Anderson; *University of Muenster, Muenster, Germany* — M. Block; *Medical University, Heidelberg, Germany* — J. Brachmann; *University of California, Irvine, Medical Center, Orange* — M. Brodsky; *Santa Rosa Memorial Hospital, Santa Rosa, Calif.* — P. Chang-Sing; *Rose Medical Center, Denver* — A. Cohen; *Memorial Hospital, Penrose St. Francis Healthcare System, Colorado Springs, Colo.* — K. Curry; *Morristown Memorial Hospital, Morristown, N.J.* — J. Curwin; *Piedmont Hospital, Georgia Baptist Medical Center, Atlanta* — T. Deering; *Medical College of*

Virginia, Richmond — K. Ellenbogen; *Bowman Gray School of Medicine, Winston-Salem, N.C.* — D. Fitzgerald; *St. Elizabeth's Hospital, Boston* — C. Haffajee; *Veterans Affairs Medical Center, Portland, Oreg.* — B. Halperin; *Christ Hospital, Cincinnati* — R. Henthorn; *Scripps Memorial Hospital, La Jolla, Calif.* — S. Higgins; *Riverside Methodist Hospitals, Columbus, Ohio* — J. Hummel; *Jackson Memorial Hospital, Miami, Fla.* — A. Interian; *Illinois Masonic Medical Center, Chicago* — R. Kehoe; *Montefiore Hospital, Bronx, N.Y.* — S. Kim; *Baystate Medical Center, Springfield, Mass.* — J. Kirchoffer; *St. Joseph's Hospital of Atlanta, Atlanta* — H. Kopelman; *St. John's Hospital, Detroit* — M. Lehmann; *Albany Medical Center Hospital, Albany, N.Y.* — J. Nattama; *St. Vincent Hospital and Medical Center, Portland, Oreg.* — D. Oseran; *Washington Hospital Center, Washington, D.C.* — E. Platia; *University Hospital, Denver* — M. Reiter; *Lankenau Hospital, Wynnewood, Pa.* — S. Rials; *Froedtert Memorial Lutheran Hospital, Milwaukee* — J. Roth; *Newark Beth Israel Medical Center, Newark, N.J.* — S. Rothbart; *Jewish Hospital, St. Louis* — J. Rottman; *Wadsworth Veterans Affairs Medical Center, Los Angeles* — P. Sager; *University of Minnesota Hospital, Minneapolis* — S. Sakaguchi; *Moffitt and Long Hospital, San Francisco* — M. Scheinman; *Jewish Hospital, Louisville, Ky.* — I. Singer; *Barnes Hospital, St. Louis* — J. Smith; *Stanford University Medical Center, Stanford, Calif.* — R. Sung; *Labey Clinic, Burlington, Mass.* — F. Venditti; *University of California Davis Medical Center, Sacramento* — Z. Vera; and *Texas Arrhythmia Institute, Houston* — N. Nasir, Jr., T. Doyle.

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