Suppression of Sustained Ventricular Tachyarrhythmias: A Comparison of d,l-Sotalol With No Antiarrhythmic Drug Treatment

VOLKER KÜHLKAMP, MD, CHRISTIAN MEWIS, MD, JOHANNES MERMI, MD, RALPH F. BOSCH, MD, LUDGER SEIPEL, MD
Tübingen, Germany

Objectives. This study evaluates the clinical efficacy of d,l-sotalol in patients with sustained ventricular tachyarrhythmias.

Background. D,l-sotalol is an important antiarrhythmic agent to prevent recurrences of sustained ventricular tachyarrhythmias (VT/VF). However, evidence is lacking that an antiarrhythmic agent like d,l-sotalol can reduce the incidence of sustained ventricular tachyarrhythmias in comparison to no antiarrhythmic drug treatment.

Methods. A prospective study was performed in 146 consecutive patients with inducible sustained ventricular tachycardia or ventricular fibrillation. In 53 patients, oral d,l-sotalol prevented induction of VT/VF during electrophysiological testing and patients were discharged on oral d,l-sotalol (sotalol group). In 93 patients, VT/VF remained inducible and a defibrillator (ICD) was implanted. After implantation of the device patients were randomly assigned to oral treatment with d,l-sotalol (ICD/sotalol group, n = 46) or no antiarrhythmic medication (n = 47, ICD-only group).

Results. During follow-up, 25 patients (53.2%) in the ICD-only group had a VT/VF recurrence in comparison to 15 patients (28.3%) in the sotalol group and 15 patients (32.6%) in the ICD/sotalol group (p = 0.0013). Therapy with d,l-sotalol, amiodarone or metoprolol was instituted in 12 patients (25.5%) of the ICD-only group due to frequent VT/VF recurrences or symptomatic supraventricular tachyarrhythmias. In nine patients, 17% of the sotalol group, an ICD was implanted after VT/VF recurrence, three patients (5.7%) received amiodarone. Total mortality was not different between the three groups.

Conclusions. D,l-sotalol significantly reduces the incidence of recurrences of sustained ventricular tachyarrhythmias in comparison to no antiarrhythmic drug treatment.

(J Am Coll Cardiol 1999;33:46–52)
©1998 by the American College of Cardiology

D,l-sotalol is a beta-adrenergic blocking drug with class 3 antiarrhythmic properties (1). Since the results of the CAST and the ESVEM study were published, d,l-sotalol has become one of the most important drugs for the treatment of sustained ventricular tachyarrhythmias (2–5). However, it is unknown whether the clinical efficacy of d,l-sotalol in patients with life-threatening sustained ventricular tachyarrhythmias can be predicted by programmed electrical stimulation. The efficacy of d,l-sotalol in preventing stimulation-induced arrhythmias may be due to its class 3 antiarrhythmic activity (6–9). However, the prevention of a spontaneous recurrence of a sustained ventricular tachycardia or ventricular fibrillation may however be related to its beta-blocking effects. Data from the ESVEM study suggest that the clinical efficacy of d,l-sotalol with programmed electrical stimulation is underestimated (4).

One nonrandomized open study compared the clinical efficacy of d,l-sotalol in patients with sustained ventricular tachyarrhythmias. It turned out that neither the response to programmed electrical stimulation nor the response of spontaneous arrhythmias to oral d,l-sotalol during 24 h Holter monitoring predicted the clinical efficacy of the compound during follow-up (10,11). Therefore, current data on d,l-sotalol emphasize that the clinical efficacy of d,l-sotalol may be substantially different from what is seen during electrophysiological testing (5,12).

The major problem with antiarrhythmic drug studies in patients with life-threatening ventricular tachyarrhythmias is the lack of a control group for ethical reasons. Furthermore, several studies suggest that persisting inducibility is associated with a poor prognosis (13). Therefore, we believe that despite ineffectiveness during electrophysiological testing, treatment with an antiarrhythmic drug cannot be justified. However, in patients with an implantable cardioverter defibrillator, antiarrhythmic therapy is not mandatory and even if it fails the arrhythmia will be terminated by the implanted device. Therefore we conducted a prospective randomized study with d,l-sotalol in patients with sustained ventricular tachyarrhythmias and an implantable cardioverter defibrillator to elucidate the clinical efficacy of d,l-sotalol in comparison to no antiarrhythmic medication.
Methods

This is an open labelled, prospective, randomized study in patients with organic heart disease and unstable symptomatic sustained ventricular tachycardia or aborted sudden cardiac death.

Patient selection. From January 1988 to December 1995, 432 consecutive patients with sustained ventricular tachycardia or aborted sudden death were seen in our department. The inclusion criteria were: 1) symptomatic sustained ventricular tachycardia or ventricular fibrillation in the presence of organic heart disease, not associated with an acute event like myocardial infarction, electrolyte disturbance etc.; 2) inducible sustained ventricular tachyarrhythmia; 3) no contraindications to treatment with beta-adrenergic blocking drugs; 4) no contraindications to treatment with an implantable cardioverter defibrillator (ICD); 5) tolerance of d,l-sotalol during in hospital treatment; and 6) no prior treatment with amiodarone. 286 patients (66.2%) were excluded from participation in the study. The reasons for exclusion were as follows: 25 patients were excluded during the initial phase of the study, because they had nonsyncopal sustained ventricular tachycardia. At that time, implantation of an ICD seemed not appropriate in nonsyncopeal ventricular tachycardia. Twenty-five patients received electrophysiologicaly guided antitachycardia surgery or catheter ablation as the initial therapy because they had frequent episodes of hemodynamically tolerated ventricular tachycar-
dia. In 136 patients, overall prognosis was limited, due to old age, advanced heart disease, or severe concomitant disease and ICD therapy was not thought to be appropriate. Contraindications to therapy with betablocking agents (mainly chronic obstructive pulmonary disease) was present in 61 patients. In 21 patients, the index arrhythmic event occurred during treatment with class 1 or class 3 antiarrhythmic drugs; 75 patients had received amiodarone prior to admission to our hospital. Forty-seven patients had incessant ventricular tachycardia or frequent episodes of nonsustained and/or sustained ventricular tachycardia and antiarrhythmic therapy seemed to be mandatory. Forty-one patients had sustained ventricular tachycardia without structural heart disease. ICD therapy seemed not to be appropriate in these patients due to the excellent prognosis of patients with idiopathic ventricular tachycardia (14). In 31 patients, no arrhythmia was induced during programmed electrical stimulation, 21 patients declined ICD implantation or electrophysiologicaly testing, 11 patients did not tolerate d,l-sotalol or developed torsades de pointes during the initial treatment phase. In about one third of the patients, more than one criterion led to exclusion from the study. Finally, 146 patients (128 men and 18 women, 33.8% of the total population seen at our department) aged 21 to 72 years (64 ± 13 years) with inducible sustained ventricular tachycardia (n = 105, 71.9%) or inducible ventricular fibrillation (n = 41, 28.1%) were included in the study and followed for at least one year. Inducible ventricular fibrillation was accepted as an arrhythmia of clinical relevance in patients with aborted sudden death. The arrhythmia history was symptomatic sustained monomorphic ventricular tachycardia in 94 patients (64.4%) and cardiac arrest in 52 patients (35.6%). The characteristics of the patients evaluated are listed in Table 1. All patients received coronary angiography and 138 patients (94.5%) had a

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>D,l-sotalol (n = 53)</th>
<th>ICD/d,l-sotalol (n = 46)</th>
<th>ICD (n = 47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 16</td>
<td>59 ± 18</td>
<td>64 ± 17</td>
<td>0.36</td>
</tr>
<tr>
<td>Gender</td>
<td>7⃣ (13.2%), 46⃣ (86.8%)</td>
<td>6⃣ (13%), 40⃣ (87%)</td>
<td>5⃣ (10.6%), 42⃣ (89.4%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>n = 39 (73.6%)</td>
<td>n = 31 (67.4%)</td>
<td>n = 28 (59.6%)</td>
<td>0.64</td>
</tr>
<tr>
<td>DCM</td>
<td>n = 11 (20.7%)</td>
<td>n = 13 (26.3%)</td>
<td>n = 16 (34%)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>n = 3 (5.7%)</td>
<td>n = 2 (4.3%)</td>
<td>n = 3 (6.4%)</td>
<td></td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I/II</td>
<td>n = 44 (83%)</td>
<td>n = 39 (84.8%)</td>
<td>n = 41 (87.2%)</td>
<td>0.84</td>
</tr>
<tr>
<td>NYHA III</td>
<td>n = 9 (17%)</td>
<td>n = 7 (15.2%)</td>
<td>n = 6 (12.8%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular EF, %</td>
<td>37 ± 17%</td>
<td>35 ± 18%</td>
<td>38 ± 19%</td>
<td>0.72</td>
</tr>
<tr>
<td>Presenting arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>VT n = 38 (71.7%)</td>
<td>VT n = 26 (56.5%)</td>
<td>VT n = 30 (63.8%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>SD n = 15 (28.3%)</td>
<td>SD n = 20 (43.5%)</td>
<td>SD n = 17 (36.2%)</td>
<td></td>
</tr>
<tr>
<td>VT cycle length (ms)</td>
<td>304 ± 32 ms (n = 19)</td>
<td>298 ± 34 ms (n = 14)</td>
<td>321 ± 44 ms (n = 15)</td>
<td>0.23</td>
</tr>
<tr>
<td>Inducible arrhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>n = 42 (79.2%)</td>
<td>n = 32 (70%)</td>
<td>n = 31 (66%)</td>
<td>0.31</td>
</tr>
<tr>
<td>VF</td>
<td>n = 11 (20.8%)</td>
<td>n = 14 (30%)</td>
<td>n = 16 (34%)</td>
<td></td>
</tr>
<tr>
<td>VT cycle length</td>
<td>287 ± 31 ms</td>
<td>281 ± 42 ms</td>
<td>279 ± 32 ms</td>
<td>0.59</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; DCM = dilative cardiomyopathy; VT = ventricular tachycardia; VF = ventricular fibrillation; SD = sudden death; EF = ejection fraction. *Only patients in whom an ECG with the spontaneous tachycardia was available.
left ventricular angiogram. The majority of patients had coronary artery disease (n = 98, 67.1%) or dilated cardiomyopathy (n = 40, 27.4%). Left ventricular ejection fraction was depressed (<45%) in 123 patients (84.2%) and ranged from 13% to 65% (37 ± 19%). For termination of prior antiarrhythmic medication or treatment with d,l-sotalol, patients were admitted to the coronary care unit or the intensive care unit. All antiarrhythmic drugs were discontinued for five elimination half-lives before entry into the study.

**Study protocol.** In patients with sustained ventricular tachycardia or aborted sudden death whose arrhythmia could be induced by programmed ventricular stimulation, the efficacy of oral d,l-sotalol in preventing stimulation-induced sustained ventricular tachyarrhythmias was investigated. If the arrhythmia was rendered noninducible by d,l-sotalol, the patient was discharged and followed on an outpatient basis (sotalol group). If the arrhythmia remained inducible, the patient received an ICD. Before implantation of the device, the patient was randomized to open label treatment with d,l-sotalol (ICD/sotalol group) or to no antiarrhythmic drug treatment (ICD-only group). Again patients were followed on an outpatient basis. All patients were followed up for at least one year. The primary end point was the recurrence of arrhythmias (ventricular tachycardia, ventricular fibrillation, or sudden death) and the time to arrhythmia recurrence in our three patient groups. Secondary end points were drug tolerance and total mortality.

Informed consent was obtained from all patients, the study protocol was approved by the local ethical committee.

**Electrophysiological study.** Programmed ventricular stimulation with up to three extrastimuli at four basic drive cycle lengths (500 ms, 430 ms, 375 ms, and 330 ms) was performed in all patients. If necessary, the ventricular stimulation protocol was repeated with a catheter placed in the right ventricular outflow tract. The end point of our ventricular stimulation protocol was reproducible (twice) induction of the clinical arrhythmia, i.e., sustained ventricular tachycardia in patients with a history of sustained ventricular tachycardia or aborted sudden death or induction of ventricular fibrillation in patients with aborted sudden death.

**Oral d,l-sotalol administration.** All patients received 80 mg d,l-sotalol as the initial daily dose. If tolerated, the dose was increased in steps of 80 mg per 24 h up to 400 mg per 24 h. Tolerance of d,l-sotalol was judged on clinical criteria such as dizziness, development of congestive heart failure or spontaneous recurrence of ventricular tachyarrhythmias.

**Efficacy criteria of electrophysiological testing.** Patients undergoing electrophysiological study while receiving oral d,l-sotalol were studied at steady state after receiving a stable dose for at least 72 h. The ventricular stimulation protocol and the end points were identical to those used in the baseline investigation. Only complete suppression of inducible nonsustained or sustained ventricular tachyarrhythmias was accepted as success. Patients in whom the ventricular tachyarrhythmia remained inducible despite oral application of oral d,l-sotalol received an ICD.

Randomized sotalol treatment in ICD recipients. After recovery from implantation of the device patients received randomized oral treatment with d,l-sotalol or no antiarrhythmic treatment. If necessary, patients in the ICD-only arm received metoprolol for control of sinus tachycardia. Oral verapamil in combination with digoxin was prescribed in patients with chronic or paroxysmal atrial fibrillation.

Ventricular arrhythmias occurring in the first week after implantation of the device were disregarded in analysis, since they might be mainly related to the implantation procedure itself (15,16).

**Follow-up and definition of end points.** Patients with an ICD were seen on an outpatient basis every three months. Patients in the sotalol group were seen at least twice in a year, or the well-being of the patient and adherence to the therapy was confirmed by a telephone call to the patient’s private practitioner (n = 2).

End points of our study protocol were as follows: 1) Recurrence of ventricular tachycardia or ventricular fibrillation after discharge from hospital: in patients with oral d,l-sotalol, a recurrence of ventricular tachycardia was defined as spontaneous sustained ventricular tachycardia, or syncope, or aborted sudden death or sudden death. In patients with an ICD, a recurrence of ventricular tachycardia or ventricular fibrillation was defined as a symptomatic (palpitations, dizziness, syncope) arrhythmic event followed by an intervention of the ICD. Appropriateness of ICD therapy was verified independently by two cardiologists experienced in ICD therapy (V.K. and C.M.). 2) Intolerance of the treatment with d,l-sotalol, i.e. overt cardiac failure, symptomatic hypotension or bradycardia. 3) Death: A time-based definition of sudden death was used. Sudden death, i.e. death within one hour after the occurrence of symptoms (17). Sudden death was assumed to be an arrhythmic death even if no intervention of the ICD was stored at the presumed time of death. Cardiac death, i.e. death of cardiac origin, not fulfilling the criteria for sudden cardiac death (17). Noncardiac death, i.e. death not primarily due to cardiac causes (17).

**Data analysis.** The statistics package of JMP Version 3.1.6.2. (SAS Institute, Cary, North Carolina) was used for data analysis. Paired data before and after application of d,l-sotalol were analyzed using the paired t test, for comparison of more than two groups the one way ANOVA test (with post test if the p value was <0.05) was used. All values are expressed as mean ± 1 standard deviation. Group comparison was done using the Chi-square test and applying Yates correction were appropriate. Survival fractions were calculated using the Kaplan–Meier method, survival curves were compared by the log-rank method. All analysis were performed on the intention to treat basis.

**Results.**

**Patient characteristics and baseline electrophysiological findings (Table 1).** There were no significant differences in the clinical presentation of patients in whom d,l-sotalol suppressed
the arrhythmia and patients in whom the arrhythmia remained inducible.

In the baseline electrophysiological study, a sustained monomorphic ventricular tachycardia was inducible in 105 patients. In 41 patients ventricular fibrillation was the only inducible arrhythmia. Baseline electrophysiological characteristics and type of induced arrhythmia were not different between patients who responded to d,l-sotalol and those who did not respond to the drug (Table 1).

Electrophysiological effects of oral d,l-sotalol. With the oral d,l-sotalol treatment, a significant increase in sinus cycle length (from 851 ± 171 ms to 1045 ± 178 ms), QT-interval (from 388 ± 39 ms to 453 ± 50 ms), the effective refractory period of the right ventricle (from 240 ± 28 ms to 278 ± 39 ms), and the cycle length of the ventricular tachycardia (from 298 ± 47 ms to 334 ± 47 ms) was achieved. The electrophysiological effects of d,l-sotalol and the daily oral dose of d,l-sotalol were not different between patients in whom the arrhythmia was rendered noninducible and patients in whom the arrhythmia remained inducible. In 53 patients (36.3%), complete suppression of inducible sustained or nonsustained ventricular tachyarrhythmias was achieved (d,l-sotalol 330 ± 89 mg/day).

ICD therapy. In 93 patients (63.7%) d,l-sotalol (348 ± 78 mg per day) did not suppress inducible sustained ventricular tachyarrhythmias, and an ICD was implanted. The first seven patients received an epicardial lead system, thereafter only transvenous lead systems were used. Due to the rapid change in ICD technology, different types of devices were implanted. The use of transvenous lead systems, devices with biphasic shock capability, antitachycardia pacing and stored electrograms was not significantly different between the two groups. 83.8% had a device capable of storing electrograms.

Long term efficacy of d,l-sotalol. A complete follow-up is available for all patients included in the study. Follow-up duration is not different between the three study groups.

In the sotalol group, 12 patients (22.6%) had a recurrence of sustained symptomatic ventricular tachycardia (n = 10) or ventricular fibrillation (n = 2). One female patient developed recurrent syncope with documented torsades de pointes after an otherwise uneventful follow-up of almost two years. Six patients (11.3%) died during follow-up in the sotalol group, two patients died suddenly (Fig. 1 and 2). Hence, 15 patients (28.3%) out of 53 patients reached a primary end point.

In the ICD/sotalol group, 14 patients (30.4%) had a recurrence of the ventricular tachycardia (n = 9, 19.6%) or ventricular fibrillation (n = 5, 10.9%), in all cases successfully terminated by the device. Multiple shocks provoked by recurrent torsades de pointes were seen in one patient, who did not have a recurrence of his baseline arrhythmia. Incessant ventricular tachycardia was observed in a further patient. Therefore 15 patients (32.6%) out of 46 patients had reached the primary end point.

In the ICD-only group, 24 patients (51.1%) had a recurrence of ventricular tachycardia (n = 17, 36.2%) or ventricular fibrillation (n = 7, 14.9%). One patient suddenly died, unwit-
Total mortality (Figure 2). Total mortality was not different between the three groups. In the sotalol only group, two patients died suddenly, one patient died from progressive heart failure and one patient from recurrent myocardial infarction.

In the ICD/sotalol group four patients (8.7%) died, two patients died suddenly. In both patients, only R-R intervals from the ICD were available. In one of these two patients, four episodes of ventricular fibrillation within one hour were terminated by the ICD, a fifth episode was not terminated by five consecutive 34J monophasic shocks. In the second patient, ventricular fibrillation was probably terminated with the second 34J shock. However the patient died instantaneously. Autopsy was declined in both patients. One patient died from heart failure.

In the ICD-only group, two patients died from pump failure and one after a recurrent myocardial infarction. One patient had autopsy-proven lethal pulmonary embolism seven days after implantation of an ICD with a transvenous lead system.

Tolerance of d,l-sotalol. In the sotalol group, the drug had to be withdrawn in three patients due to hemodynamic intolerance or Bradycardia. A reduction of the prescribed oral dose of d,l-sotalol by the patient or the private practitioner was noted in five patients. However, only one had a recurrence of sustained ventricular tachycardia.

Significant bradycardia and hypotension led to discontinuation of d,l-sotalol in two patients of the ICD/sotalol group. In two further patients, the dose of oral d,l-sotalol was decreased by the patient.

Change of therapy. An ICD was implanted in nine patients due to symptomatic sustained ventricular tachyarrhythmias (VT/VF) recurrence (including the female patient with tordades des pointes) or recurrent aborted sudden death in the sotalol group. Three patients switched to amiodarone. Therefore, a change of therapy was necessary in 12 patients (22.6%).

A change of therapy was necessary in two patients (4.3%) in the ICD/sotalol group. In the patient with tordades des pointes, d,l-sotalol was withdrawn, one patient with frequent recurrences of ventricular tachycardia switched to amiodarone.

A change of therapy was necessary in 12 patients (25.5%) in the ICD-only group. Therapy with d,l-sotalol was instituted in five patients. Due to frequent recurrences of sustained ventricular tachycardia, six patients were treated with metoprolol for supraventricular arrhythmias and one patient received amiodarone for control of ventricular arrhythmias. The need for a change of the treatment regimen was significantly (p = 0.0047) different between the three study groups.

Discussion

The main findings of our study are: recurrences of sustained ventricular tachyarrhythmias were significantly reduced by d,l-sotalol in comparison to no antiarrhythmic drug treatment. So-called responders and nonresponders to d,l-sotalol during programmed electrical stimulation have a comparable incidence of recurrences of ventricular tachyarrhythmias during follow-up (Fig. 1).

Clinical efficacy of d,l-sotalol. The present study is the first one comparing the clinical efficacy of d,l-sotalol in responders and nonresponders during electrophysiological testing to an untreated patient group. D,l-sotalol, even if ineffective during electrophysiological testing, turned out to be superior in terms of arrhythmia suppression in comparison to no antiarrhythmic treatment during long term follow-up. We therefore recommend treatment with d,l-sotalol in patients with an ICD to reduce the number of therapies delivered by the device. Similar reports have been published, showing that betablocker treatment decreases the relative risk of receiving a shock by the ICD (18). It is, however, contrary to a study with various class 1 and class 3 antiarrhythmic agents, that could not find any benefit of adjunctive antiarrhythmic therapy in patients with an ICD (19).

Since the introduction of parallel testing by Brugada and Wellens, it is well known that the clinical efficacy of an antiarrhythmic drug may differ from what is seen during programmed electrical stimulation (20,21). With amiodarone, it has been shown that the clinical efficacy may be higher than would have been predicted by the results of programmed electrical stimulation (22–24). Like d,l-sotalol, amiodarone is not a pure class 3 antiarrhythmic drug and its clinical efficacy cannot be explained by its antiarrhythmic effects only (12,25).

In the ESVEM trial d,l-sotalol was more effective during follow up than various class 1 antiarrhythmic drugs, although electrophysiological testing and Holter monitoring would have predicted a similar efficacy. This finding supports our theory that the clinical efficacy of a complex compound like d,l-sotalol cannot be predicted by electrophysiological testing. Empirical treatment with d,l-sotalol might lead to results comparable to those obtained with amiodarone (26). In one uncontrolled trial, neither the response to Holter monitoring nor the response to programmed electrical stimulation predicted the clinical efficacy of d,l-sotalol (11). One recent study suggests that programmed electrical stimulation is useful in predicting the efficacy of sotalol therapy (27). However, the group of patients treated with sotalol, despite inefficacy of the drug during the electrophysiological study, is small.

Value and shortcomings of programmed electrical stimulation. The recurrence of sustained ventricular tachycardia or ventricular fibrillation was not significantly different between patients in whom d,l-sotalol prevented induction of a VT/VF and patients in whom d,l-sotalol failed to prevent induction of a sustained ventricular tachyarrhythmia. Hence, electrophysiological testing underestimates the clinical efficacy of the drug. Similar data have been obtained with nadolol in patients with sustained ventricular tachycardia (28). However, a much larger patient population is necessary to prove our hypothesis that electrophysiologic testing is not useful for prediction of efficacy in the case of d,l-sotalol.

In our study, about one third of the patient population in the sotalol-only group had a recurrence of VT/VFs despite a positive (i.e., suppression of sustained ventricular arrhythmias) result of electrophysiological testing. This is in contrast with many studies reporting a low risk for recurrence of ventricular
tachycardia or ventricular fibrillation if the arrhythmia is not inducible (7–9,29–32). However, in most of these studies, a limited number of patients are treated for a short period of time and a control group is lacking in all studies.

There may be several reasons why the response to programmed electrical stimulation fails to predict the clinical efficacy of d,l-sotalol: day to day variability in induction of VT/VF varies, especially if induction of the arrhythmia requires stimulation with more than two extrastimuli and multiple sites (33,34).

Another important point is that, during programmed electrical stimulation, the class 3 effects of d,l-sotalol on the reentry circuit are mainly tested since it has been shown that a pure beta-blocker does not change inducibility during programmed electrical stimulation (35,36). However, the reentry circuit in sustained ventricular tachycardia is not a fixed anatomic circuit but is amenable to changes in autonomic tone, electrolyte disturbances, stretch, ischemia, and not least, varying levels of the antiarrhythmic drug itself. Beta-blockade interacts with the autonomic nervous system (37), increases the fibrillation threshold (38) and reduces ischemia (39), factors which might trigger the induction of VT/VF (36). The importance of these effects cannot be assessed by programmed electrical stimulation. Therefore not only the results of the baseline study vary, the same is true for the electrophysiological study on antiarrhythmic drugs (33). We recently performed programmed electrical stimulation in patients, in whom d,l-sotalol prevented induction of a sustained ventricular tachyarrhythmia after a mean follow-up of 14 ± 10 months. In 42% of patients, the initial arrhythmia was induced despite the fact that the patient had no spontaneous recurrence of the arrhythmia and the clinical situation had not changed (40).

Prognostic influence of the cardioverter defibrillator. This study is not designed to evaluate the effect of different therapeutic interventions on total mortality. Furthermore, the patient group is highly selected with about two thirds of the patients having symptomatic ventricular tachycardia. Although our numbers are small, our study does not support an approach using an ICD in all patients with sustained ventricular tachyarrhythmias as first line therapy (41,42). However, 9 out of 53 patients (17%) in the sotalol-only group switched to ICD therapy, because they had a symptomatic recurrence during treatment with sotalol. The recently published AVID trial showed that ICD therapy is superior to antiarrhythmic drug therapy in prolonging survival among patients with life-threatening ventricular tachyarrhythmias (43).

Limitations of the study. Some uncertainty about arrhythmia recurrences in our three study groups remains. In the sotalol group only symptomatic recurrences could be documented, hence it is possible that we underestimated the true incidence of recurrences in this group. On the other hand we probably overestimate the number of recurrences in both ICD arms. Some episodes might have terminated spontaneously or symptomatic supraventricular tachycardia activated the device. However, this should have occurred in similar frequency in both ICD arms. There is indeed a larger number of recurrences in the ICD/sotalol group as compared to the sotalol-only group. This difference is not significant. However, with the number of patients included in our study, a difference of clinical significance between responders to d,l-sotalol and nonresponders to d,l-sotalol cannot be ruled out. A further limitation is the dose of sotalol. A higher dose of sotalol might have changed the clinical efficacy of the drug (27).

Finally, for further evaluation of the value of electrophysiological testing in the case of d,l-sotalol, a double blind study comparing d,l-sotalol and placebo with an ICD as backup is necessary in a much larger group of patients.

Conclusions. We conclude that d,l-sotalol is effective in terms of arrhythmia suppression in comparison to no antiarrhythmic treatment even if it fails to prevent stimulation induced ventricular tachyarrhythmias. Hence treatment with d,l-sotalol in ICD patients is recommended to prevent recurrences of ventricular tachyarrhythmias. However, further studies are needed to finally learn the value or lack of electrophysiological testing.

References


