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Long-Term Follow-Up of Patients With Short QT Syndrome

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Objectives The aim of this study was to investigate the clinical characteristics and the long-term course of a large cohort of patients with short QT syndrome (SQTS).

Background SQTS is a rare channelopathy characterized by an increased risk of sudden death. Data on the long-term outcome of SQTS patients are not available.

Methods Fifty-three patients from the European Short QT Registry (75% males; median age: 26 years) were followed up for 64 ± 27 months.

Results A familial or personal history of cardiac arrest was present in 89%. Sudden death was the clinical presentation in 32%. The average QTc was 314 ± 23 ms. A mutation in genes related to SQTS was found in 23% of the probands; most of them had a gain of function mutation in HERG (SQTS1). Twenty-four patients received an implantable cardioverter defibrillator, and 12 patients received long-term prophylaxis with hydroquinidine (HQ), which was effective in preventing the induction of ventricular arrhythmias. Patients with a HERG mutation had shorter QTc at baseline and a greater QTc prolongation after treatment with HQ. During follow-up, 2 already symptomatic patients received appropriate implantable cardioverter defibrillator shocks and 1 had syncope. Nonsustained polymorphic ventricular tachycardia was recorded in 3 patients. The event rate was 4.9% per year in the patients without antiarrhythmic therapy. No arrhythmic events occurred in patients receiving HQ.

Conclusions SQTS carries a high risk of sudden death in all age groups. Symptomatic patients have a high risk of recurrent arrhythmic events. HQ is effective in preventing ventricular tachyarrhythmia induction and arrhythmic events during long-term follow-up. (J Am Coll Cardiol 2011;58:587–95) © 2011 by the American College of Cardiology Foundation

The association between long QT interval and sudden death has been known for more than 50 years (1), but only recently has interest moved to the opposite, a short QT interval. In 1993, Algra et al. (2) observed that both prolonged and shortened corrected QT (QTc) intervals were associated with an increased risk of sudden death (SD) compared with intermediate QTc values. In 2000, Gussak et al. (3) reported a family with short QT intervals (QTc <300 ms) and atrial fibrillation (AF) in 1 of the members and an unrelated woman with similar electrocardiography (ECG) changes who died suddenly. Finally, our group in 2003 recognized the short QT syndrome (SQTS) as a new clinical entity related to familial SD with an autosomal dominant inheritance (4), and the genetic nature of the disease was confirmed shortly after (5–8). Although the upper limit of normal QT values is well defined, the lower limit has not been determined to date. In the initial published cases of SQTS, the QT and the QTc were constantly 300 ms or less. In the subsequent years, individuals with SQTS and QTc values of <340 ms were reported in association with SD (9). According to population studies, QTc of 360 ms or less or QT of 88% or less of the predicted QT (QTp) have been proposed as the lower limit of the normal QTc and QT, because these correspond to the mean values minus 2 standard deviations in the general population (10).

The first proposed therapy was an implantable cardioverter-defibrillator (ICD). Some studies have demonstrated the efficacy of hydroquinidine (HQ) over a short-term

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Abbreviations and Acronyms

AF = atrial fibrillation
CA = cardiac arrest
ECG = electrocardiography
EPS = electrophysiological study
ERP = effective refractory period
HQ = hydroquinidine
ICD = implantable cardioverter-defibrillator
QTc = corrected QT
QTp = predicted QT
SD = sudden death
SQTS = short QT syndrome
VF = ventricular fibrillation

period and in a limited number of patients (11,12). As SQTS has been recognized only recently, data regarding the long-term outcomes of SQTS patients are not available. The purposes of this study were, first, to assess the clinical presentation, the electrocardiographic features, and the prevalence of known genetic mutations and their relationship with the long-term prognosis in a large cohort of SQTS patients and, second, to verify the efficacy and the side effects of the therapy, including ICD and antiarrhythmic drugs.

Methods

Study population. From June 2002, SQTS patients from 7 European centers were enrolled in the European SQTS Registry. In the present study, we included patients with a QTc of 360 ms or less (or ≤88% of QTp) associated with history of SD or aborted SD or syncope of arrhythmic origin. Subjects with a very short QT interval (QTc ≤340 ms) were included even if they were asymptomatic. Family members of affected patients having a short QT interval also were included in the study. The final study group comprised 53 patients (75% males; median age: 26 years; interquartile range: 17 to 39 years) from 29 proband-identified families. Thirty-three patients already have been reported in previous studies (4,9,11,13–15).

Four patients were included after SD, having ECG documentation of short QT intervals before cardiac arrest. There were 27 cases of SD without ECG documentation in the families, which therefore were not included in the present study.

Data collection and management. For each patient, data on personal and family history, cardiac events, and therapy were recorded. Between 1 and 8 (median: 2) 12-lead ECG with a paper speed of 25 or 50 mm/s and a gain of 10 mm/mV were available and were analyzed for each patient. The ECG parameters were measured with a 400% magnification from the lead with the highest T-wave amplitude, usually V_2 or V_3, by 3 independent examiners. Analyzed ECG parameters were: heart rate, QRS interval duration, QT interval, QTc, and QTp according to Rautaharju et al.'s formula (16). Moreover, Jpoint–Tpeak, Q–Tpeak, Tpeak–Tend, and Tpeak–Tend/QT ratio were evaluated. The QT interval was measured manually according to the tangential method; the Tpeak was measured from the highest point of the T wave. Comparing the mean QT values obtained with tangential (282 ± 39) and threshold (291 ± 42) methods by paired *t* test, we found a statistically significant difference (−9.1 ± 14; p = 0.0001), however, with an excellent agreement between the 2 methods (Pearson correlation coefficient [*r*] = 0.94). It is already known that the first method slightly underestimates the QT interval; however, it has a similar or higher reproducibility (17); moreover, we consider it particularly appropriate in SQT patients because of the high-voltage T waves.

A baseline electrophysiological study (EPS) was performed in 28 patients. In 8 patients, EPS was repeated during oral HQ administration after the steady-state concentration was reached.

Altogether, 24 patients received an ICD and 12 patients received long-term prophylaxis with HQ. One patient was treated with amiodarone.

Follow-up. The follow-up time comprised historical clinical information from birth to enrollment and the prospective follow-up information at 6-month intervals from enrollment through November 2010. Of the 53 patients, 4 died before clinical evaluation; 1 child died during the follow-up at 4 months of age of noncardiac causes. The parents of a child with ventricular fibrillation (VF) declined to take part in the follow-up.

Statistical analysis. Comparisons between groups were carried out with the chi-square test or Fisher exact test for qualitative variables, and the 1-way analysis of variance (ANOVA) or the *t* test for quantitative variables apart from variables that have a skewed distribution and for which the nonparametric Kruskal-Wallis or Mann–Whitney rank-sum tests were used. We applied the Bonferroni correction to address the problem of multiple comparisons. Parameters before and after treatment were compared using the paired *t* test or the Wilcoxon matched-pairs signed-rank tests. The Kaplan–Meier product-limit estimator was used to compare event incidence between different patient subgroups. The log-rank or Wilcoxon tests were used to test the statistical significance of the observed differences. To exclude that the patients treated with HQ may be at higher or lower risk based on other characteristics, we performed a comparison of baseline clinical and demographic characteristics (gender, age, previous events, and QTc at baseline) between the 2 groups. The multivariate logistic regression was performed with Firth correction to avoid the problem of separation resulting from having no event in HQ. All the tests were 2 tailed. A value of $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical data. Thirty subjects (24 males [80%]; median age: 23 years; interquartile range: 17 to 34 years) initially came to the observation for the following reasons: SD (n = 4), aborted SD (n = 13), syncope (n = 4), other symptoms (palpitations: n = 3; effort dyspnea: n = 1), family screening for SD (n = 3), and ECG results recorded for other reasons (n = 2). Fifteen patients had a history of familial SD (50%).

After the screening of the related families, 23 subjects were added to the study population, 16 of whom were male,

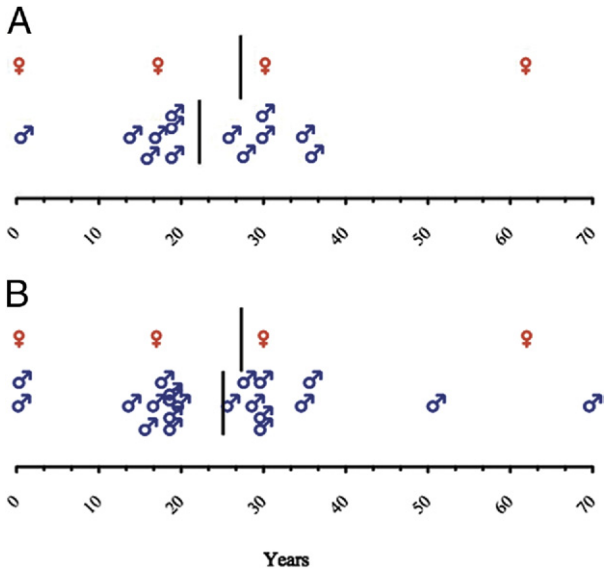

Figure 1 Cardiac Events in Males and Females

Graph showing the age distribution of **(A)** sudden death and **(B)** sudden death or syncope in males (♂) and females (♀).

with a median age of 32 years (interquartile range: 21 to 42 years). Considering the entire population, 33 of 53 patients had symptoms at presentation (62%): 4 had died suddenly, 13 had an aborted SD (range: 3 months to 62 years), 8 had syncope, 13 had palpitations (6 of whom had documented AF or flutter). Frequent ventricular ectopic beats were documented in 6 patients.

Two pediatric patients were affected by severe congenital multiorgan disease; no cardiac involvement or acquired causes that could determinate a short QT interval were detected in any of these cases.

Cardiac arrest (CA) had a similar prevalence in males and females (35% vs. 30%; p = 0.15), and in both genders, episodes at <1 year of age were reported. In males, more than 90% of CA events occurred between 14 and 40 years of age, whereas in females, the events were spread across the entire lifespan; syncope was observed only in males and had a similar age distribution (Fig. 1).

In the patients carrying a HERG mutation, a greater proportion of affected females (55% vs. 18%; p = 0.04) and a higher prevalence of AF (36% vs. 3.6%; p = 0.02) were observed compared with non-HERG patients.

Genetic analysis. Genetic analysis was performed in 22 of the index patients and revealed a mutation in 5. Four families had a mutation in HERG, N588K in 2 (5) and T618I in the other 2, a Chinese family (13) and a white family (unpublished data from C. Antzelevitch group, Masonic Medical Research Laboratory, Utica, New York): both the mutations were in the pore loop of the HERG channel. A family had a mutation in CACNB2b (8). The test results were negative in 12 index patients, whereas in 5 cases, the analysis was still ongoing at the time of writing.

ECG. In all the available ECG, the average QT was 76 ± 6% of the QTp (range: 59% to 86%); the average QT interval was 282 ± 39 ms and the QTc was 314 ± 23 ms (range: 250 to 350 ms).

No differences were found in the ECG parameters between symptomatic and asymptomatic patients (Table 1). A Brugada type 1 ECG and a shorter than normal QT interval were found in 3 patients: in 2 brothers with a CACNB2b mutation and a history of CA in 1, the pattern was observed after ajmaline challenge (8). The third case was a 30-year-old man who sought treatment after a nocturnal syncope and showed a spontaneous type 1 ECG.

Comparing the ECG parameters between patients with a mutation in HERG with those without such a mutation, QT interval, QTc, QT/QTp, Jpoint–Tpeak, Tpeak–Tend, and Tpeak–Tend/QT ratio were significantly shorter in HERG patients (Table 2).

Electrophysiological study. Twenty-eight patients underwent an EPS. The ventricular effective refractory periods (ERPs) at the right ventricular apex at a cycle length of 600 to 500 ms were shortened and varied between 140 and 200 ms (mean: 166 ± 21 ms). No differences were found between patients with a history of CA or syncope and those without (right ventricular apex, S1S1 500 ms: 158 ± 15 ms vs. 148 ± 18 ms; p = 0.21). VF was induced in 16 patients

Table 1 Comparison of Electrocardiographic Parameters Between Patients With Previous Cardiac Arrest, Patients With Syncope, and Asymptomatic Patients

	All Patients (n = 53)	Cardiac Arrest (n = 18)	Syncope (n = 8)	No Cardiac Arrest or Syncope (n = 27)	p Value
HR (beats/min)	78 ± 21	79 ± 20	73 ± 14	79 ± 23	0.68
QRS (ms)	82 ± 9	84 ± 5	83 ± 5	80 ± 11	0.22
QT (ms)	282 ± 39	278 ± 44	289 ± 34	283 ± 38	0.68
QTc (ms)	314 ± 23	311 ± 25	316 ± 23	315 ± 22	0.80
QT/QTp (%)	76 ± 6	75 ± 6	76 ± 6	77 ± 5	0.46
J–Tpeak (ms)	121 ± 29	113 ± 35	123 ± 36	126±23	0.51
Q–Tpeak (ms)	205 ± 34	197 ± 44	210 ± 35	208 ± 28	0.76
Tp–Te (ms)	77 ± 16	78 ± 14	80 ± 13	75 ± 19	0.79
Tp–Te/QT(%)	27 ± 5	28 ± 5	28 ± 6	26 ± 5	0.44

Values are mean ± SD.
HR = heart rate; J–Tpeak = Jpoint to T-wave peak; Q–Tpeak = Q to T-wave peak; QRS = QRS interval; QTc = corrected QT; QTp = predicted QT; Tp–Te = T-wave peak to T-wave end.

Table 2 Comparison of Electrocardiographic Parameters Between Patients With Mutation in HERG and Those Without Mutation in HERG

	HERG (n = 11)	Non-HERG (n = 28)	p Value
HR (beats/min)	88 ± 21	73 ± 13	0.02
QRS (ms)	85 ± 13	82 ± 4	0.34
QT (ms)	253 ± 26	292 ± 32	0.0003
QTc	297 ± 29	319 ± 17	0.01
QT/QTp (%)	72 ± 7	77 ± 5	0.03
J–Tpeak (ms)	103 ± 22	125 ± 26	0.007
Q-Tpeak (ms)	187 ± 35	208 ± 27	0.05
Tp–Te (ms)	66 ± 10	85 ± 13	0.0002
Tp–Te/QT (%)	26 ± 6	29 ± 5	0.011

Values are mean ± SD.
Abbreviations as in Table 1.

(57%): 3 had an aborted SD and 5 had syncope. Seven (44%) of the 16 had mechanical induction of VF during catheter positioning. In 12 patients, ventricular tachyarrhythmias were not induced: 5 had an aborted SD and 2 had syncope. Because only 3 of the 8 patients with a history of CA had inducible VF, EPS sensitivity was only 37%, and its negative predictive value was 58%. The atrial ERPs also were shortened and ranged between 120 and 200 ms (mean: 163 ± 22 ms). AF was induced in 8 patients (36%). Comparing the electrophysiological parameters between patients with a mutation in HERG (n = 7) and those without (n = 12), the ventricular ERPs were shorter in the first group (151 ± 14 ms vs. 176 ± 24 ms; p = 0.01).

Therapy. HYDROQUINIDINE. In 22 patients, HQ was tested to assess its efficacy in prolonging the QT interval. In 6 cases, it was discontinued early because of poor therapeutic compliance, in 2 cases because no effect on the QT was observed, whereas 2 subjects (9%) reported gastroenteric side effects. Twelve patients (8 adults and 4 children) had been receiving HQ for a mean period of 76 ± 30 months (range: 27 to 105 months); the mean dosage in adults was 870 ± 186 mg per day (range: 600 to 1,000 mg per day). ECG before and after drug therapy were available for analysis from 18 patients (Table 3). In 8 patients, the EPS was repeated after the drug had reached the steady-state concentration, in 6 cases via the ventricular lead of the ICD. Ventricular ERPs were prolonged significantly (from 154 ± 12 ms to 205 ± 23 ms; p = 0.02). Seven patients had VF induced at baseline (87%), whereas none had VF induced after HQ (p = 0.016). Comparing the ECG parameters in patients with mutation in HERG with those without such a mutation, the effect of HQ on QTc was more relevant and constant in the first group, both in N588K and in T618I carriers (Table 3, Fig. 2).

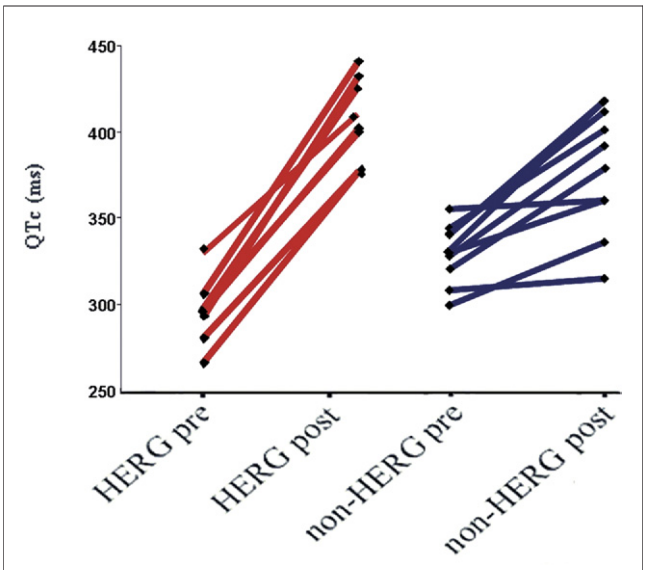

Figure 2 Different Effect of Hydroquinidine in Patients With HERG Mutation Versus Those Without HERG Mutation

Effect of hydroquinidine on the corrected QT (QTc) in patients **(left)** with a HERG mutation compared with **(right)** those without a HERG mutation. Pre = before treatment; post = during treatment.

OTHER DRUGS. Experiences with drugs other than HQ are reported in Table 4.

Amiodarone. Amiodarone was administered in 2 patients. It did not produce any effect on the QT interval in a woman with an HERG mutation. Another patient (male; QTc: 350 ms) with documented VF at the age of 26 years and unknown genotype (Figs. 3 and 4) received amiodarone and metoprolol: the QTc was prolonged to 400 ms and no arrhythmias were recorded in a 6-month follow-up. Previous treatment with

Table 3 Comparison of Electrocardiographic Parameters Before and After Initiation of Hydroquinidine in 18 Patients

	All Patients (n = 18)	HERG (n = 8)	Non-HERG (n = 10)	Difference Between HERG and Non-HERG (p Value)
QTc before HQ	307 ± 20	299 ± 23	313 ± 17	
QTc after HQ	384 ± 39	404 ± 30	362 ± 36	
Difference (p value)		105 ± 14	49 ± 9	56 ± 16 (p = 0.004)
QT/QTp before HQ	73 ± 5	71 ± 5	75 ± 4	
QT/QTp after HQ	91 ± 9	96 ± 7	86 ± 7	
Difference (p value)		25 ± 3	11 ± 2	14 ± 4 (p = 0.006)

Values are mean ± SE.
Abbreviations as in Table 1.

Table 4 Patients With Available Data to Compare the Efficacy of Hydroquinidine With Other Antiarrhythmic Treatments

Patient Age, Gender, HERG Status	Drug	Dosage	HR (beats/min)	QT (ms)	QTc (ms)	QT/QTp (%)
31 yrs, female, HERG	Basal ECG		86	250	300	71
	Amiodarone	200 mg	71	260	284	68
	Sotalol	80 mg twice daily	63	280	287	70
	Hydroquinidine	250 mg thrice daily	85	360	428	102
35 yrs, male, HERG	Basal ECG		66	270	283	68
	Sotalol	80 mg twice daily	63	260	266	65
	Hydroquinidine	250 mg thrice daily	60	380	380	93
71 yrs, female, HERG	Basal ECG		77	291	329	79
	Disopyramide	400 mg/day	86	299	358	85
	Hydroquinidine	500 mg twice daily	75	342	382	91
44 yrs, female, HERG	Basal ECG		70	292	315	76
	Disopyramide	400 mg/day	79	290	333	79
	Hydroquinidine	500 mg twice daily	81	318	370	88
43 yrs, male, non-HERG	Basal ECG			290	338	80
	Disopyramide	100 mg twice daily	95	290	365	86
	Hydroquinidine	300 mg twice daily	97	270	343	81
29 yrs, male, non-HERG	Basal ECG		81	300	349	83
	Sotalol	80 mg thrice daily	54	350	332	82
	Amiodarone	200 mg twice daily	60	400	400	98

ECG = electrocardiography; other abbreviations as in Table 1.

sotalol was ineffective both in prolonging the QT interval and in preventing ventricular tachyarrhythmias.

Disopyramide. Three patients with inducible VF at baseline, 1 who was asymptomatic with unknown genotype and 2 with paroxysmal AF and HERG mutation, underwent an antiarrhythmic drug trial with oral disopyramide (200 to 400 mg per day). VF was still inducible in the patient taking the lower dosage, and no changes were observed in the ventricular ERPs. In the patients taking the higher dosage, the QTc prolonged slightly (Table 4), and the ventricular ERP prolonged from 160 to 200 ms in 1 case; these latter data have been reported already (18).

Follow-up. Forty-seven patients were followed up over 64 ± 27 months (Fig. 5).

PATIENTS WITH A PREVIOUS CARDIAC ARREST. Twelve patients had an aborted SD. An ICD was implanted in 11 patients. One child with an HERG mutation (4) had CA at the age of 8 months, with severe neurologic damage. He did not undergo ICD implantation and received HQ from the age of 6 years, which effectively prolonged the QT interval. Two patients started HQ at the time of ICD implantation, which was discontinued after a few days in 1 patient (9).

During follow-up, 1 patient repeatedly received appropriate shocks on VF and was treated with amiodarone with success. One patient received inappropriate ICD shocks because of atrial flutter; he underwent successful cavotricuspid isthmus ablation and was started on oral HQ. One patient had 2 asymptomatic episodes of polymorphic nonsustained ventricular tachycardia.

PATIENTS WITH A HISTORY OF SYNCOPE. Eight patients had syncope at presentation: 4 received an ICD, 3 declined the ICD, and in 1 case, the patient was judged to be at low risk (a 23-year-old man with no familial history of SD and probably vasovagal syncope). Of the 3 patients who declined the implant, one was a 70-year-old man with permanent AF and familial history of SD who declined any treatment; the others were 2 brothers with a family history of SD with an unknown genotype and inducible VF during EPS, who received HQ (9).

The only event during the follow-up occurred in a patient with a HERG mutation (SQTS1) who received an appropriate shock on VF 11 months after the implantation. He was a 16-year-old male with syncope at the age of 8 months and a family history of SD over 3 generations (4,14).

PATIENTS ASYMPTOMATIC FOR CARDIAC ARREST OR SYNCOPE. Twenty-seven patients were asymptomatic for CA and syncope. Eight of them had AF or palpitations. An ICD was implanted in 9 patients because of a family history of SD, induction of VF at EPS, or both (9,13). Seven patients also received HQ, but it was soon interrupted in 5 patients. Oral HQ alone was started in 2 adult patients with family history of SD who stopped it early and in a 25-year-old patient with permanent AF (15). Moreover, HQ therapy was started in 3 children (2 younger than 1 year), and the drug was well tolerated (9).

During follow-up, 1 patient experienced a syncope, and 2 other patients had episodes of nonsustained ventricular tachycardia documented by the ICD: none of them were receiving pharmacological prophylaxis (9).

The event rate in the whole population was 3.3% per year. All the events occurred in patients who were not receiving HQ: in this group, the event rate was 4.9% per year, whereas no arrhythmic events occurred in those receiving HQ (Fig. 6). In a multivariate analysis (Table 5), only the QTc was

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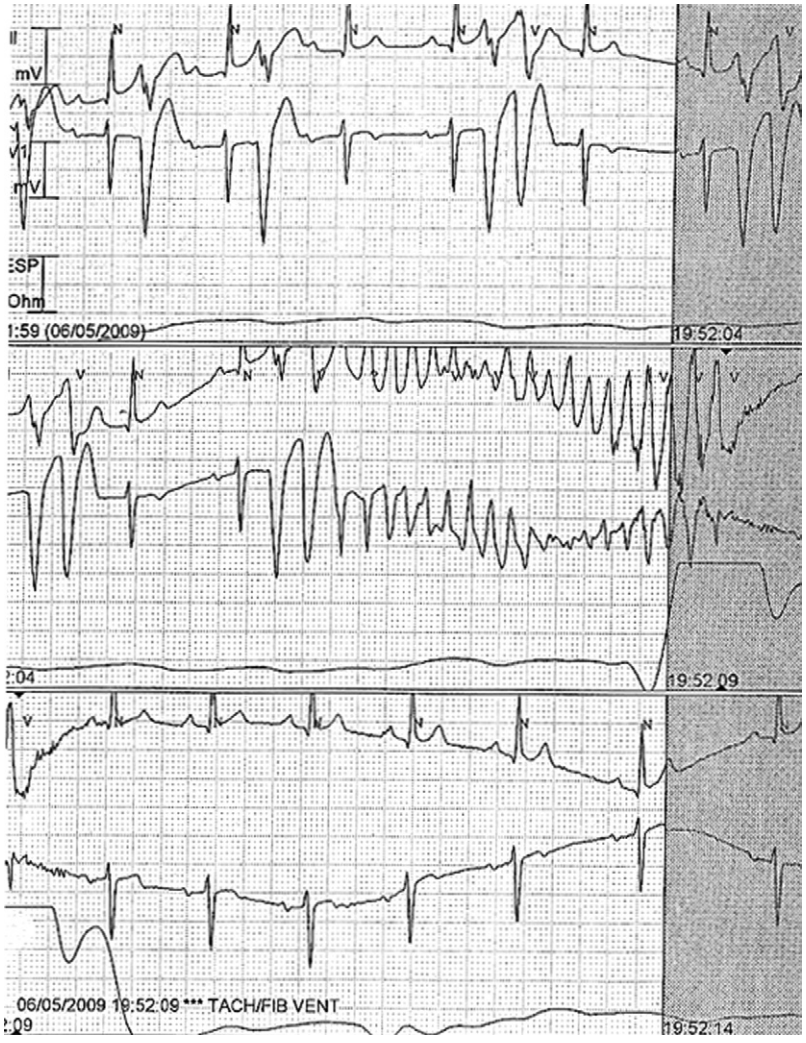

Figure 3 **Nonsustained Ventricular Tachycardia**

Polymorphic nonsustained ventricular tachycardia recorded in a patient with history of sudden death and repeated shocks of the implantable cardioverter-defibrillator (Holter monitoring; paper speed, 25 mm/s).

significantly different between the 2 groups, with a shorter mean QTc before therapy in the group receiving HQ.

ICD-RELATED COMPLICATIONS. Fourteen patients (58%) of 24 had complications related to the ICD. In 8 subjects, inappropriate shocks were observed: 4 patients with a HERG mutation received inappropriate shocks shortly after implantation (within 2 months) because of T-wave oversensing (19). No recurrences were reported after the new programming of the ICD. The other 4 patients had inappropriate shocks during episodes of supraventricular tachycardia. Three patients had ICD lead replacement because of lead fracture, and a fourth patient had ICD lead replacement because of an infection of the ICD system; 1 patient had early substitution of the ICD because of a recall. One had severe psychological distress.

Discussion

In the present study, the long-term outcome of 53 patients with SQTS is reported, representing the largest series in the literature. Clinical characteristics, therapy efficacy, and the outcome after the diagnosis were analyzed. The follow-up was almost complete, with only 1 patient not participating. Almost 90% of the patients had a personal or familial history of SD at presentation. A prevalence of males was observed, and the mean age was between 20 and 30 years. More than 60% of the subjects had symptoms at presentation: the most frequent symptom was CA, which represented the first clinical manifestation in one third of the patients. It was observed also in infants in their first months of life. Most of the events occurred in males, mainly between the second and the fourth decade. This distribution

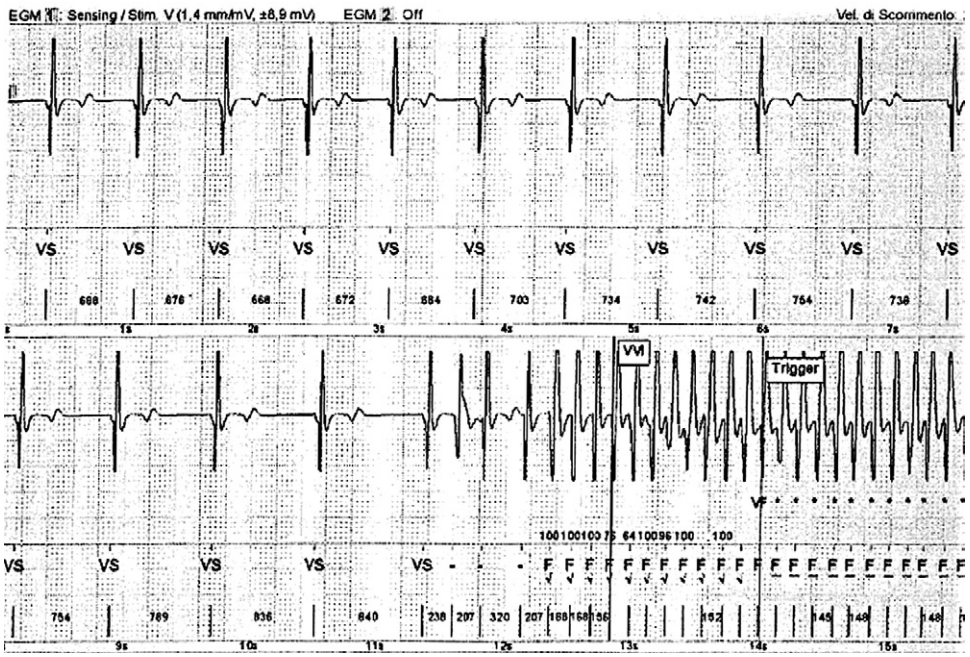

Figure 4 Ventricular Fibrillation Recorded by the Implantable Cardioverter-Defibrillator

Same patient as in Figure 3. The arrhythmia is triggered by a short-coupled ventricular extrasystole.

of events corresponds to the age with the highest testosterone plasma levels (20). Androgens, and specifically testosterone, cause a shortening of the QT in boys after puberty, which is responsible for the fact that women exhibit QTc intervals significantly longer than men (21). These hormonal influences may provide relative protection to post-puberal boys and men in the context of the long QT syndrome (22). However, the possible relationship of testosterone with suscep-

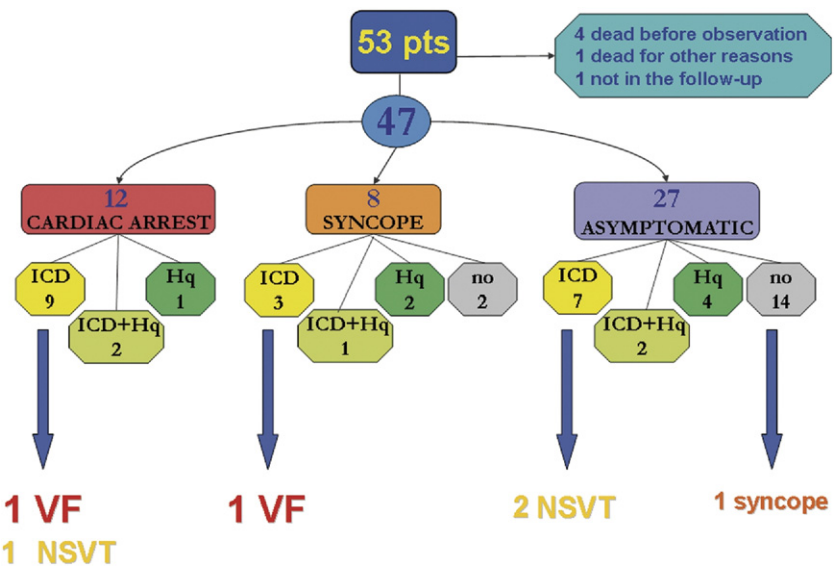

Figure 5 Therapeutic Approach

Schematic representation of therapeutic approach and follow-up of the entire population. Hq = hydroquinidine; ICD = implantable cardioverter-defibrillator; NSVT = nonsustained ventricular tachycardia; pts = patients; VF = ventricular fibrillation.

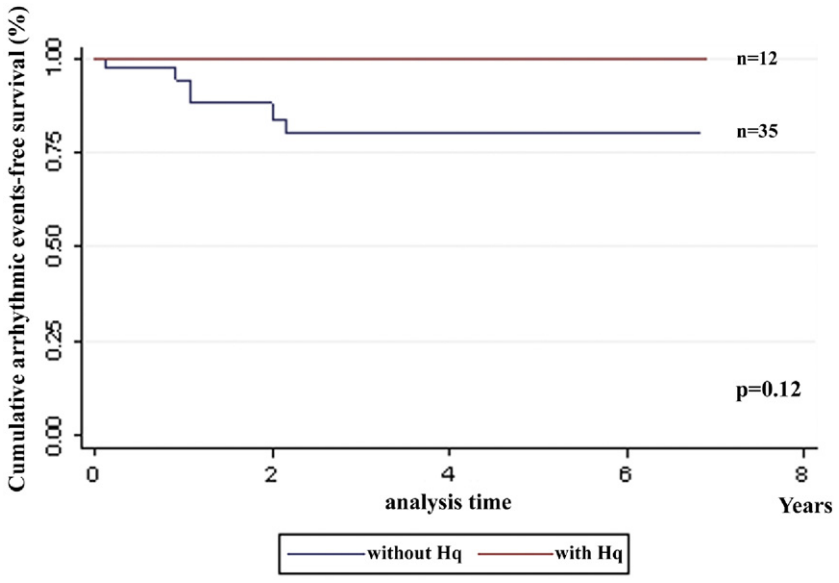

Figure 6 **Different Incidence of Arrhythmic Events in Patients Treated With Hydroquinidine and Without Therapy**

Kaplan-Meier estimate of survival free of major arrhythmic events during a 5-year follow-up in a comparison of patients treated with hydroquinidine (Hq) with those without therapy. The difference is not statistically significant.

tibility for cardiac arrhythmias in the context of SQTS needs to be investigated further. Syncope was the second most frequent clinical manifestation, in 15% of cases. The finding of several episodes of nonsustained ventricular tachycardia recorded by the ICD or during telemetry in our patients seems to confirm that self-terminating episodes of VT or VF may be the cause of syncope in SQTS (Figs. 3 and 4). CA and syncope occurred both at rest and during effort, so that it was not possible to identify a uniform trigger for the events. AF or atrial flutter were observed in 15% of the population, also younger than 35 years.

Concerning the ECG parameters, we considered a consistently short QT interval (QTc ≤340 ms) among the inclusion criteria in the study (9), even in the absence of symptoms or family history of SD. Moreover, we decided to include also patients with a QTc of 360 ms or less and a history of SD or aborted SD or syncope of arrhythmic origin. In this larger population, the previous observation (9) that the QTc values in a population with short QT did not distinguish between asymptomatic subjects and those with CA was confirmed. In a recent paper by Anttonen et al. (23), it was shown that parameters such as the Jpoint–Tpeak interval and Tpeak–Tend/QTc may differentiate patients with SQTS and CA from asymptomatic subjects with a shorter than normal QT interval from the general population. None of these indexes, however, could discriminate, in our population of patients with SQTS, asymptomatic SQT subjects from those with CA or syncope (Table 1). Furthermore, EPS was not useful in predicting CA, having a sensitivity of only 37%.

Table 5 **Comparison of Baseline Clinical and Demographic Characteristics Between Patients Receiving Hydroquinidine and Those Not Receiving Hydroquinidine**

	HQ (n = 12)	No HQ (n = 35)	p Value
Male (%)	9 (75%)	28 (80%)	0.70*
Age at first visit	27 ± 21	32 ± 18	0.41†
Symptomatic for CA or syncope (%)	6 (50%)	14 (40%)	0.74*
CA (%)	3 (25%)	9 (26%)	0.99*
Syncope (%)	3 (25%)	5 (14%)	0.40*
Asymptomatic (%)	6 (50%)	21 (60%)	0.74*
QTc at baseline	302 ± 23	320 ± 20	0.01†

Values are n (%) or mean ± SD. *Fisher exact test. †*t* test.
CA = cardiac arrest; HQ = hydroquinidine; other abbreviations as in Table 1.

The yield of genetic screening in SQTS was 23% of the investigated index patients. Mutations predominantly were found in KCNH2/HERG (4 of the 5 with a positive genotype), whereas a loss of function mutation in the CACNB2b gene was found in another family. Patients with a HERG mutation constituted a subgroup with specific characteristics such as a greater proportion of affected females and a higher prevalence of AF compared with non-HERG patients. Moreover, they exhibited shorter QT intervals and ERPs.

HQ was tested in 41% of the patients. In the patients with a HERG mutation, HQ induced normalization of the QT interval and of the ERPs, whereas in those without the mutation, a weaker effect and a significant variability of responses were observed. HQ prevented the induction of

ventricular arrhythmias during EPS in all studied patients, and none of the treated patients had arrhythmic events during the follow-up. Drug tolerability was good: Only 9% of the patients interrupted it because of side effects (gastroenteric intolerance or dermatitis). HQ was used in adults mainly as a prophylaxis for AF or flutter, but also in patients who had declined an ICD implant and in children both as primary and secondary prevention after VF. HQ served as a valuable bridge to ICD. However, unfortunately quinidine became no longer available in several European countries for commercial reasons (24).

The incidence of arrhythmic events during the follow-up was 4.9% per year in the patients without pharmacological prophylaxis, whereas no arrhythmic events occurred in those receiving HQ. VF occurred in already symptomatic patients. No events were recorded among treated patients, even if previously symptomatic. For this reason, HQ may be considered as an alternative option to ICD in patients who cannot receive it (children) or who decline the implant, but it is still underused. Fifty-eight percent of the patients with an ICD had complications related to the device. Many were inappropriate shocks, secondary to T-wave oversensing with double counting of the R and T waves, which occurred early after the implant (19) and were prevented with correct ventricular sensitivity programming for VF detection.

Future perspectives. The current study included only asymptomatic patients if they had very short QT intervals. In the future, it would be important to expand this registry, including also asymptomatic subjects with borderline short QT intervals, to understand better the prognosis and to help guide the management of such patients.

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