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Hydroquinidine Prevents Life-Threatening Arrhythmic Events in Patients With Short QT Syndrome

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ABSTRACT

BACKGROUND Short QT syndrome (SQTS) is a rare and life-threatening arrhythmogenic syndrome characterized by abbreviated repolarization. Hydroquinidine (HQ) prolongs the QT interval in SQTS patients, although whether it reduces cardiac events is currently unknown.

OBJECTIVES This study investigated whether long-term treatment with HQ reduces the occurrence of life-threatening arrhythmic events (LAE) (cardiac arrest or sudden cardiac death) in SQTS patients.

METHODS In this cohort study on consecutive SQTS patients, 2 analyses were performed: 1) a matched-period analysis for the occurrence of LAE in 17 SQTS patients who received long-term HQ; and 2) a comparison of the annual incidence of LAE off- and on-HQ in 16 SQTS patients who survived a cardiac arrest.

RESULTS A total of 17 patients (82% male, age 29 ± 3 years, QTc before treatment 331 ± 3 ms) received HQ therapy (584 ± 53 mg/day). Therapy was stopped in 2 cases (12%) due to gastrointestinal intolerance, and 15 patients continued treatment for 6 ± 1 year. QTc prolongation was observed in all patients (by 60 ± 6 ms; $p < 0.001$). We compared the occurrence of LAE during 6 ± 1 years before and after HQ, observing that patients on HQ experienced a reduction in both the rate of LAE from 40% to 0% ($p = 0.03$) and the number of LAE per patient from 0.73 ± 0.3 to 0 ($p = 0.026$). Furthermore, the annual rate of LAE in the 16 patients with a previous cardiac arrest dropped from 12% before HQ to 0 on therapy ($p = 0.028$).

CONCLUSIONS We demonstrated for the first time that treatment with HQ was associated with a lower incidence of LAE in SQTS patients. These data point to the importance that quinidine, that in several countries has been removed from the market, remains available worldwide for patients with SQTS. In the present study, therapy with HQ has been proven to be safe, with a relatively low rate of side effects. (J Am Coll Cardiol 2017;70:3010–5) © 2017 by the American College of Cardiology Foundation.

Short QT syndrome (SQTS) is one of the most malignant and rare inherited arrhythmogenic disorders, with <200 cases reported worldwide (1–3). Early studies demonstrated that hydroquinidine (HQ) is able to prolong the duration of QT interval and to prevent the induction of ventricular arrhythmias at programmed electrical stimulation in SQTS patients (2). These observations have led to the off-label use of HQ to prolong the QT interval in SQTS patients. Despite the lack of information on

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whether the drug also exerts an antiarrhythmic effect, clinical guidelines now recommend HQ treatment in SQTS patients (4). The objective of this study was to assess whether HQ therapy is able to reduce life-threatening arrhythmic events (LAE) in patients with SQTS during a long-term follow-up.

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METHODS

TERMS AND DEFINITIONS. In accordance with the recommended definition (4), SQTS was diagnosed in the presence of a QTc interval ≤340 ms, or a QTc interval between 341 and 360 ms accompanied by 1 or more of the following clinical parameters: history of cardiac arrest (CA) or arrhythmic syncope, a family history of unexplained CA at a young age (≤40 years of age), or a family history of SQTS.

The term "life-threatening arrhythmic event" (LAE) was used to refer to sudden cardiac death and aborted CA (i.e., ventricular fibrillation [VF] requiring defibrillation to be terminated).

Symptomatic patients were defined as individuals who have survived 1 or more LAE.

Electrocardiographic terms were as follows: *baseline electrocardiogram (ECG)* was the 12-lead ECG recorded at first visit, prior to starting HQ; *first ECG on therapy* was the first ECG recorded after initiation of HQ, after the maximum tolerated dose of HQ was chronically administered.

HQ was administered with a starting dose of 3 mg/kg/day and was gradually increased to reach the normalization of the QTc interval (i.e., QTc >360 ms).

STUDY POPULATION. Our population included 73 individuals affected by SQTS who were offered treatment with HQ and were informed that it was unknown whether HQ would reduce the occurrence of LAE. A total of 17 of 73 patients agreed to start the treatment; 9 (53%) of them had an implantable cardioverter-defibrillator (ICD).

Clinical data for the patients included in the study were stored in a custom database developed by the information technology team of our institution (V.T., R.B.).

STUDY DESIGN AND STATISTICAL ANALYSIS. Statistical analysis was performed (E.P., V.B.) using SPSS software version 21 (IBM, Armonk, New York) and R version 3.0 (R Foundation, Vienna, Austria). In general, continuous variables were expressed as mean ± SE; categorical variables were reported as absolute and relative frequencies. Comparisons between continuous variables were performed with paired and unpaired nonparametric tests, as appropriate. Comparisons between categorical variables were performed with McNemar and Fisher tests, as appropriate.

To assess the effects of HQ on LAE, we performed 2 analyses, applying the specific methodology illustrated in the following text:

Matched period analysis on the population treated with HQ. For each patient treated with HQ, we defined the duration of the follow-up on HQ as the *observation time on-therapy* and the period of identical duration before starting therapy with HQ as the *observation time off-therapy* with patients serving as their own controls. The percentage of symptomatic patients and the mean number of LAE per patient in the 2 observation periods were compared by McNemar and Wilcoxon tests, respectively.

Comparison of the annual rate of LAE in symptomatic patients treated with HQ versus untreated. Here we included only patients (n = 16) who had survived an LAE before diagnosis, and we compared the occurrence of LAE at follow-up in the 6 treated patients and the 10 untreated patients. We applied the modified Kaplan-Meier method suggested by Snapinn et al. (5), which estimates the cumulative hazard rates of events according to the presence or absence of treatment. The analysis was performed by assigning the 16 symptomatic patients to the "nontreatment group" for the period from enrollment prior to initiation of HQ and then subsequently assigning them to the "treatment group" for the period from the initiation of HQ until the end of follow-up. The antiarrhythmic effect of HQ was evaluated by comparing the rate of LAE while off-HQ to the rate of LAE while on-HQ for each of the 16 patients. The LAE rate was calculated, and the Poisson exact conditional test performed to compare the 2 rates (6). A value of $p < 0.05$ (2-sided) was considered statistically significant.

ABBREVIATIONS AND ACRONYMS

CA = cardiac arrest
ECG = electrocardiogram
HQ = hydroquinidine
ICD = implantable cardioverter-defibrillator
LAE = life-threatening arrhythmic events
PY = person-years
SQTS = short QT syndrome
VF = ventricular fibrillation

RESULTS

MATCHED PERIODS ANALYSIS ON THE POPULATION TREATED WITH HQ. Of the 73 SQTS patients followed up at our center, 17 (23%) accepted initiation of therapy with HQ (14 of 17 males, 82%; QTc at baseline ECG 331 ± 3 ms; age at enrollment 29 ± 3 years; age range 15.7 to 42.4 years) (Table 1). Before starting HQ, 11 of 17 (65%) individuals were asymptomatic and 6 of 17 (35%) patients had experienced 1 or more LAE (a total of 12 VF episodes were recorded in the 6 patients: 6 of 12 happened before ICD implant and required external defibrillation, whereas 6 of 12

TABLE 1 Clinical Characteristics of the 15 patients Who Received Long-Term HQ Treatment

Patient ID #	Sex	Weight (Kg)	Cardiac Events Before HQ	Family History of SD	Age of SQTS Diagnosis (yrs)	Genotype	Mutation	QTc Pre-HQ (ms)	QTc Post-HQ (ms)	ICD Implanted	HQ Start Age (yrs)	HQ Therapy Duration (yrs)	HQ Dose (mg/day)
1	Male	63	Syncope	No	15	–	–	312	398	No	16	9.5	300
2	Male	66	Asymptomatic	No	15	–	–	314	350	No	16	1.9	500
3	Female	55	Aborted cardiac arrest	(Adopted)	20	*KCNQ1*	R259H	316	405	Yes	22	11.1	750
4	Male	75	Asymptomatic	No	12	–	–	321	412	No	17	9.9	450
5	Male	84	Aborted cardiac arrest	No	27	–	–	324	418	Yes	30	4.9	450
6	Female	65	Asymptomatic	No	38	–	–	326	356	No	38	0.9	300
7	Male	83	Asymptomatic	No	35	*KCNJ2*	D172N	332	396	No	36	12.3	750
8	Male	60	Syncope	No	14	–	–	337	388	No	17	1.5	450
9	Male	85	Asymptomatic	Brother, 18 yrs	23	–	–	338	390	Yes	24	2.6	550
10	Male	76	Aborted cardiac arrest	No	34	–	–	338	398	Yes	42	7.5	500
11	Male	75	Asymptomatic	No	30	–	–	339	358	No	30	7.6	825
12	Male	70	Asymptomatic	No	21	–	–	340	382	No	22	1.4	450
13	Male	80	Aborted cardiac arrest	Uncle, 49 yrs	27	–	–	344	413	Yes	28	7.7	750
14	Male	70	Aborted cardiac arrest	No	34	–	–	348	390	Yes	35	6.9	450
15	Male	72	Aborted cardiac arrest	No	37	–	–	351	410	Yes	40	5.4	450

Cardiac events before hydroquinidine (HQ) therapy included the most severe among aborted cardiac arrest and syncope. Two additional short QT syndrome (SQTS) patients (1 male aged 26 years and 1 female aged 53 years), both carriers of an ICD, interrupted the treatment with HQ after 1 week due to gastrointestinal intolerance.

ICD = implantable cardioverter-defibrillator.

happened after ICD implant and were appropriately shocked by the device). Overall, 9 of 17 patients (53%) were carriers of an ICD. Two (12%) of the 17 individuals carried a pathogenic SQTS variant, in *KCNQ1* (Arg259His) and in *KCNJ2* (Asp172Asn), respectively; none of the others carried mutations in the 5 genes associated with SQTS.

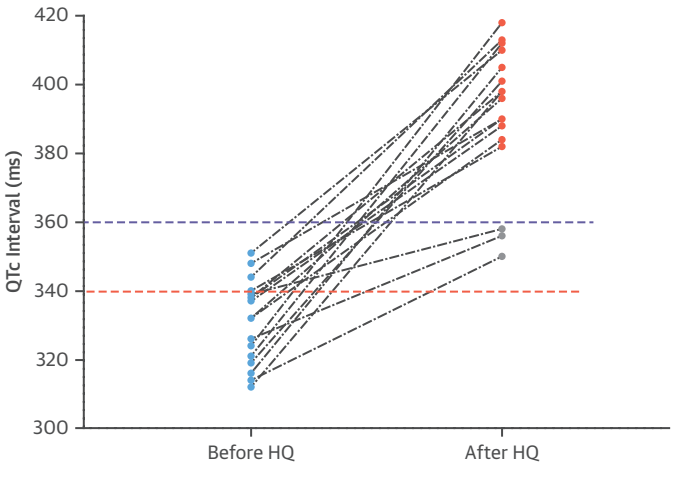
HQ was administered at a mean dose of 584 ± 53 mg/day (8 ± 1 mg/kg/day). The mean QTc at the first ECG on therapy was 391 ± 5 ms; HQ induced a mean prolongation of the QTc interval of 60 ± 6 ms ($p < 0.001$) (Figures 1 and 2). Before starting HQ, 13 of 17 (76%) patients had QTc values <340 ms, whereas none of the patients exhibited a QTc interval <340 ms during HQ therapy ($p < 0.001$). Furthermore, 14 of 17 (82%) patients had a "normal" (i.e., >360 ms) QTc interval while on HQ therapy ($p < 0.001$) (Figures 1 and 2).

Two (12%) of the 17 patients, both carriers of an ICD, interrupted the treatment after 1 week due to gastrointestinal intolerance (diarrhea). The mean duration of risk exposure during matched periods before and after HQ for the remaining 15 patients was 6 ± 1 years, for a total of 91 person-years (PY) per period.

No patients experienced any LAE after initiating HQ, leading to a dramatic reduction in both the percentage of patients with LAE and the number of LAE per patient during the treatment period (from 40% to 0; $p = 0.03$; and from 0.73 ± 0.30 to 0; $p = 0.026$, respectively).

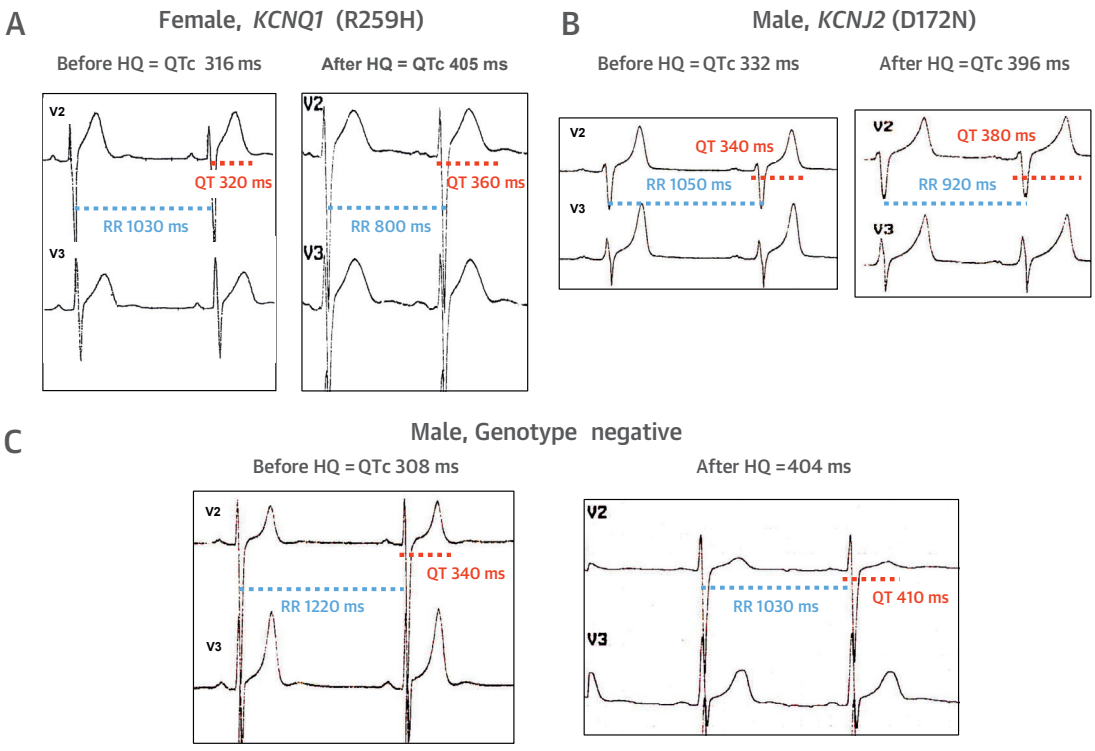
COMPARISON OF THE ANNUAL RATE OF LAE OFF- AND ON-HQ IN SQTS SYMPTOMATIC PATIENTS. This analysis was performed on 16 SQTS patients who survived 1 or more aborted CAs (14 of 16 males [88%]; QTc at baseline ECG 333 ± 4 ms; age at presentation 26 ± 3 years), 6 (38%) of whom subsequently started therapy with HQ. No statistically significant

FIGURE 1 Comparison of QTc Interval Values for 17 Patients Before and After Starting HQ



After starting hydroquinidine (HQ), the number of patients with extremely short QTc interval (i.e., <340 ms, **orange dotted line**) dropped from 76% to 0, and 82% of the patients normalized their QTc values. **Blue dots** represent QTc interval values before HQ; **orange dots** represent "normalized" QTc interval values during HQ therapy; and **gray dots** represent QTc interval values that persisted below 360 ms during HQ therapy. The **purple dotted line** represents the threshold of "normal" QTc interval (i.e., >360 ms).

FIGURE 2 Effect of HQ in 3 SQTS Patients



(A and B) The effect of hydroquinidine (HQ) on 2 genotype-positive short QT syndrome (SQTS) patients. **(A)** The effect of HQ in a woman with a gain-of-function mutation in KCNQ1 gene (R259H) and a baseline QTc of 316 ms who experienced 2 episodes of cardiac arrests before starting HQ. After starting treatment, her QTc lengthened to 405 ms and she remained asymptomatic for 11 years. **(B)** The effect of HQ in a male with a gain-of-function mutation in the KCNJ2 gene (D172N) with a baseline QTc of 332 ms. After starting HQ, his QTc lengthened to 396 ms. He has never experienced any cardiac events, and remained asymptomatic during 12 years of treatment with HQ. **(C)** The effect of HQ on a genotype-negative male patient who had a baseline QTc of 308 ms that was prolonged to 404 ms after initiation of HQ treatment. He had experienced an unexplained syncope before starting HQ and remained asymptomatic during almost 10 years of HQ treatment. **Dotted lines** indicate the intervals used to measure the electrographic parameters before and after HQ (**blue** for the RR interval, **orange** for QT interval).

differences were present between HQ-treated and untreated patients in all relevant clinical characteristics. All patients remained LAE-free while on HQ therapy, and the annual rate of LAE dropped from 12% while off-HQ (10 LAE over 82 PY) to 0 while on-HQ (0 LAE over 44 PY; p = 0.028) (**Central Illustration**).

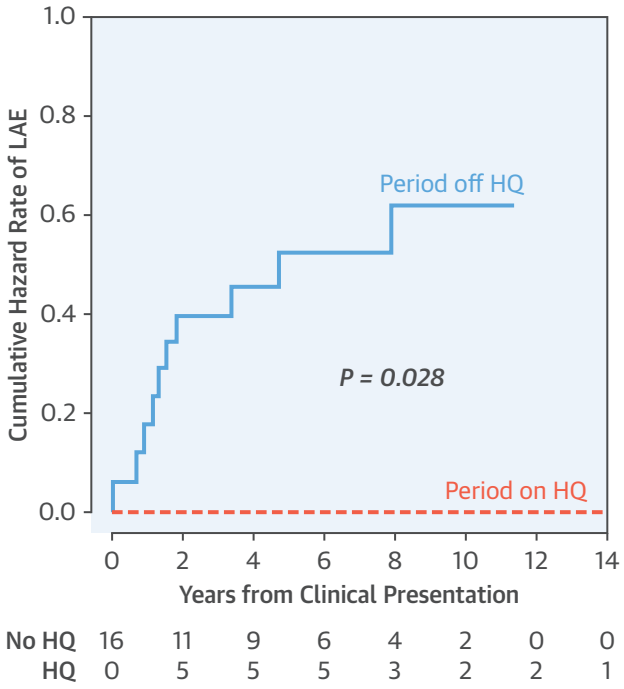
DISCUSSION

This study demonstrates for the first time the long-term antiarrhythmic efficacy of HQ for patients affected by SQTS, which is one of the rarest inherited arrhythmogenic syndromes and is associated with a high risk of experiencing life-threatening arrhythmias (with an estimated incidence of CA of 1.3%/year [3]).

Due to the low number of cases reported in the published data, it is difficult to calculate the risk of CA in SQTS patients, particularly when they present without symptoms at a young age (3). Programmed electrical stimulation has been considered "contra-indicated" (Class III) in the latest ESC guidelines for the prevention of SCD (4). Although ICD implantation is an invasive procedure often leading to severe adverse events, given the lethality of the disease, its prophylactic use remains a necessary therapeutic strategy for SQTS patients. A pharmacological approach that safely and reliably reduces arrhythmic events would be a key asset to delay or avoid early ICD implantation, and for this reason, since the original description of SQTS in 2000 (1), research has been focusing on the identification of an effective pharmacological therapy for this disease.

Analogous with the introduction of mexiletine for the management of long QT syndrome type 3 (LQT3)

CENTRAL ILLUSTRATION Cumulative Hazard of Life-Threatening Arrhythmic Events (LAE) Stratified By a Time-Varying Indicator of Hydroquinidine (HQ) Treatment in SQTS Patients



Mazzanti, A. et al. J Am Coll Cardiol. 2017;70(24):3010–5.

To explore the effect of HQ over time on the risk of LAE in short QT syndrome (SQTS) patients with a previous cardiac arrest, we used a modified Kaplan-Meier method that estimates the cumulative hazard rates of events according to the presence or absence of treatment. All patients at the beginning of observation were included in the nontreatment group **(continuous blue line),** and the assignment to the treatment group **(orange dashed line)** was updated at the time of HQ initiation. The HQ effect was evaluated in terms of LAE rate ratio (see Methods section for details). All 6 patients who were symptomatic before starting HQ remained LAE-free over 6 ± 1 years of treatment. Overall, in the group of symptomatic SQTS patients, the annual rate of LAE dropped from 12% while off HQ (10 LAE over 82 person-years) to 0 while on HQ (0 LAE over 44 person-years; $p = 0.028$).

(7,8), which was initially driven by the attempt to shorten QT interval, the use of HQ was introduced in the clinics to correct for the abnormal duration of the QT interval in SQTS patients (2). Recently, we documented that besides shortening the QTc interval, mexiletine is also able to reduce arrhythmic events in LQT3 patients (9); therefore, we decided to investigate whether HQ may exert an antiarrhythmic effect in patients with SQTS. Rationale supporting an antiarrhythmic action of quinidine in an *in-silico* model of SQTS was recently provided by Luo et al. (10). The authors used a modified ten Tusscher model (11) of human action potential incorporating the kinetics of the gain-of-function mutant N588K in the I_{Kr}-channel. The model demonstrated that simulated pharmacological actions of quinidine prolonged the action potential duration and the effective refractory period, thus reducing the susceptibility to re-entry.

In our study, the effect of HQ was particularly remarkable, as the drug was able to reduce the annual rate of LAE from 12% to 0% in the high-risk subgroup of SQTS patients who have survived 1 or more episodes of CA (3). This subgroup, as we previously reported, has a hazard rate ratio for life-threatening arrhythmic events of 37.5 when compared with asymptomatic patients ($p < 0.0001$) (3). Importantly, no pro-arrhythmic events were observed in the treatment group, thus confirming the safety of HQ for SQTS patients.

The observed rate of long-term tolerability for chronic HQ treatment was overall acceptable, and superior to that seen in other studies, such as the QUIDAM (Evaluation of the Interest of Oral Hydroquinidine Administration to Treat Patients With Brugada Syndrome, High Cardiac Arrhythmic Risk and Implanted With an Implantable Cardioverter

Defibrillator) study (12), which prescribed a higher dose of HQ in patients with Brugada syndrome and recorded a higher percentage of patients (26%) experiencing side effects, ultimately leading to the discontinuation of treatment. In our study, in fact, only 12% of patients experienced gastrointestinal side effects that required termination of HQ therapy. This good profile of tolerability is likely connected to the lower dose of HQ used (738 ± 25 mg/day in the QUIDAM study vs. 584 ± 53 mg/day in our cohort, $p < 0.001$).

STUDY LIMITATIONS. Our study is based on a small cohort of patients, and this is obviously a limitation dictated by the rarity of the disease. We believe, however, that this pilot study will support the view that HQ, a drug removed from the marked in several countries, should remain available for its lifesaving role in inherited arrhythmias that now also include SQTS (13).

CONCLUSIONS

The evidence that HQ prolongs QT interval and reduces life-threatening arrhythmias supports the view that it may be used as an additive therapy to reduce ICD shocks and possibly as an alternative therapy to the ICD implant when it is contraindicated, unavailable, or refused by patients. For comparison, the efficacy of HQ in prolonging the QT interval and preventing CA in SQTS patients parallels the ability of mexiletine to shorten the QT interval and to reduce arrhythmias in LQT3 patients (9). Together, these data provide a new paradigm for the treatment of inherited repolarization abnormalities that drives the field beyond the current focus on controlling triggers, toward the pharmacological correction of the abnormal substrate.

We hope that, based on the encouraging data provided by this study, it will be possible to gather an international partnership to define in a multicenter randomized study the role of hydroquinidine in SQTS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: SQTS is a rare inherited disorder associated with a high risk of sudden arrhythmic death. Hydroquinidine prolongs the QT interval and reduces the risk of life-threatening arrhythmias in patients with SQTS.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to validate the safety and antiarrhythmic efficacy of hydroquinidine as an adjunct or alternative to implanted defibrillator therapy in patients with SQTS.

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KEY WORDS arrhythmias, drug repurposing, hydroquinidine, short QT syndrome, sudden cardiac death